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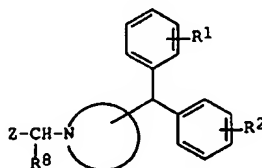
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WO 02/00631 A2

(54) Title: BENZHYDRYL DERIVATIVES



(I)

(57) Abstract: A compound of the formula (I): in which Z, R<sup>1</sup>, R<sup>2</sup>, R<sup>8</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> are each as defined in the description, or a salt thereof. The object compound of the present invention has pharmacological activities such as Tachykinin antagonism, and is useful for manufacture of a medicament for treating or preventing Tachykinin-mediated diseases.

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## D E S C R I P T I O N

## BENZHYDRYL DERIVATIVES

## 5 TECHNICAL FIELD

The present invention relates to new benzhydryl derivatives and a salt thereof.

More particularly, it relates to new benzhydryl derivatives and a salt thereof which have pharmacological  
10 activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament.

15 Accordingly, one object of the present invention is to provide new and useful benzhydryl derivatives and a salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the  
20 like.

Another object of the present invention is to provide a process for the preparation of said benzhydryl derivatives and a salt thereof.

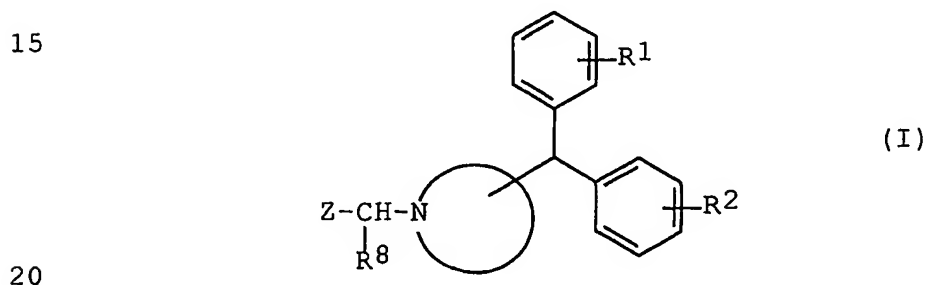
A further object of the present invention is to  
25 provide a pharmaceutical composition comprising, as an active ingredient, said benzhydryl derivatives and a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a use of said benzhydryl derivatives or a  
30 pharmaceutically acceptable salt thereof as Tachykinin antagonist, especially Substance P antagonist, Neurokinin A antagonist or Neurokinin B antagonist, useful for treating or preventing Tachykinin-mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis,  
35 cough, expectoration, and the like; ophthalmic diseases

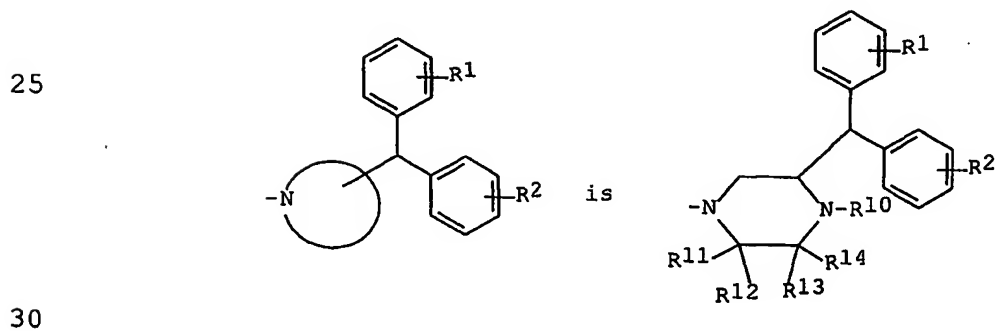
such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid  
 5 arthritis, osteoarthritis, and the like; pains or aches (e.g., migraine, headache, toothache, cancerous pain, back pain, etc.); and the like in human being or animals.

## DISCLOSURE OF INVENTION

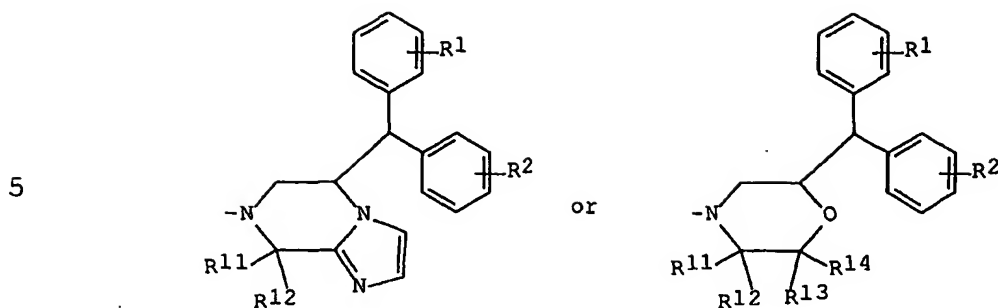
10 The object compound of the present invention can be represented by the following general formula (I):



wherein

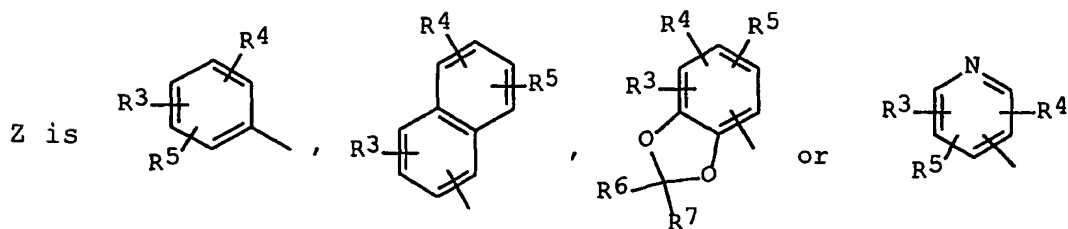


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in which  $R^1$  and  $R^2$  are independently hydrogen, halogen,  
 10 lower alkoxy, lower alkyl or mono(or di or  
 tri)halo(lower)alkyl,  
 $R^{10}$  is hydrogen or lower alkyl optionally substituted  
 with lower alkoxy, carbamoyl or phenyl,  
 $R^{11}$ ,  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  are independently hydrogen,  
 15 lower alkoxycarbonyl or lower alkyl optionally  
 substituted with hydroxy or lower alkoxy, and  
 $R^{10}$  and  $R^{14}$  optionally forming  $-(CH_2)_i-CHR^{15}-(CH_2)_j-$ ,  
 $-(CH_2)_i-NR^{16}-(CH_2)_j-$ ,  $-(CH_2)_i-O-CH_2-CO-$  or  
 $-(CH_2)_i-O-(CH_2)_j-$ , wherein  $i$  and  $j$  are independently 1  
 20 or 2,  $R^{15}$  is hydrogen, halogen, lower alkyl, hydroxy,  
 lower alkoxy, amino, lower alkylamino or  
 di(lower)alkylamino and  $R^{16}$  is hydrogen, lower alkyl,  
 lower alkanoyl, lower alkoxycarbonyl,  
 benzyloxycarbonyl, lower alkylsulfonyl or mono(or di  
 25 or tri)halo(lower)alkylsulfonyl, or  
 $R^{12}$  and  $R^{13}$  optionally forming  $-(CH_2)_i-CHR^{15}-(CH_2)_j-$ ,  
 wherein  $i$ ,  $j$  and  $R^{15}$  are defined as above, or  
 $R^{13}$  and  $R^{14}$  optionally forming oxo or two to five  
 methylenes,

30



35



in which R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently hydrogen;  
halogen; lower alkyl; mono(or di or  
tri)halo(lower)alkyl; cyano; lower alkoxy carbonyl;  
5 lower alkylthio; lower alkylsulfonyl; hydroxy; lower  
alkoxy optionally substituted with lower alkoxy, lower  
alkoxy carbonyl, carbamoyl, cyano, phenyl or one, two  
or three halogen(s); lower alkenyloxy;  
cyclo(lower)alkyloxy; nitro; lower alkylamino;  
10 di(lower)alkylamino; or imidazolyl, pyrazolyl, thienyl,  
thiazolyl, furyl, tetrazolyl, pyridyl or phenyl, each  
of which may have a substituent selected from a group  
which consists of lower alkyl, mono(or di or  
tri)halo(lower)alkyl, lower alkylsulfonyl, lower  
15 alkylsulfinyl, lower alkylthio, lower alkylamino and  
di(lower)alkylamino, and  
R<sup>6</sup> and R<sup>7</sup> are independently hydrogen or halogen, and  
R<sup>8</sup> is hydrogen or lower alkyl.

20 It is to be noted that the object compound (I) may  
include one or more stereoisomers due to asymmetric carbon  
atom(s) and double bond, and all of such isomers and a  
mixture thereof are included within the scope of the  
present invention.

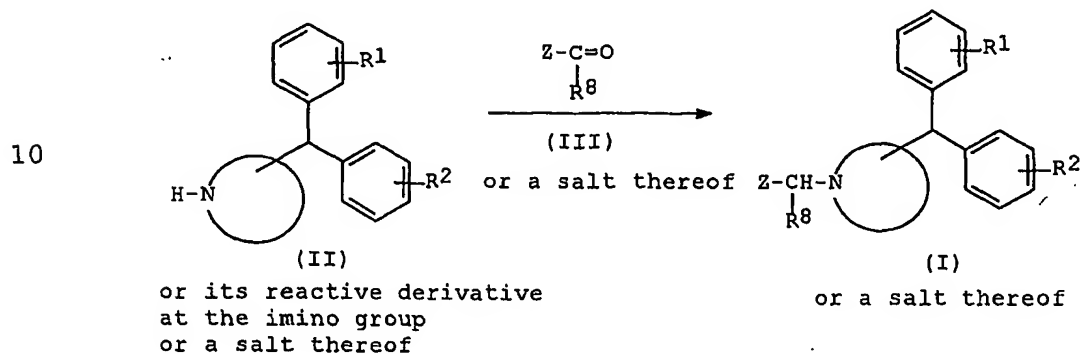
25 It is further to be noted that isomerization or  
rearrangement of the object compound (I) may occur due to  
the effect of the light, acid, base or the like, and the  
compound obtained as the result of said isomerization or  
rearrangement is also included within the scope of the  
30 present invention.

It is also to be noted that the solvating form of the  
compound (I) (e.g. hydrate, etc.) and any form of the  
crystal of the compound (I) are included within the scope  
of the present invention.

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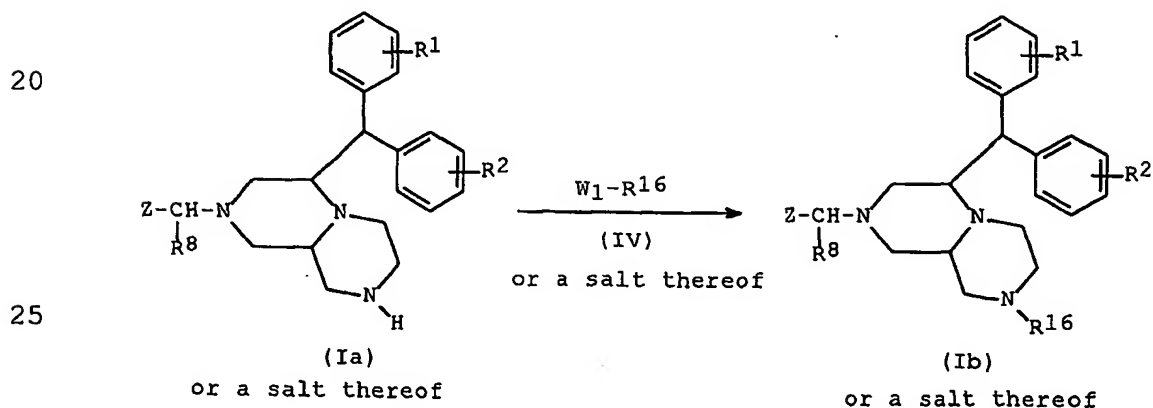
According to the present invention, the object compound (I) or a salt thereof can be prepared by processes which are illustrated in the following schemes.

### 5 Process 1



15

### Process 2



wherein

30 Z, R<sup>1</sup>, R<sup>2</sup>, R<sup>8</sup> and R<sup>16</sup> are each as defined above, and W<sub>1</sub> is a leaving group.

As to the starting compounds (II) and (III), some of them are novel and can be prepared by the procedures described in the Preparations and Examples mentioned later

35

or similar manners thereto.

Suitable salts of the starting and object compounds are conventional non-toxic and pharmaceutically acceptable salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, fumarate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise indicated.

Suitable "halogen" and "halogen" moiety in the terms "mono(or di or tri)halo(lower)alkyl", "mono(or di or tri)halo(C<sub>1</sub>-C<sub>4</sub>)alkyl", etc. may include fluorine, chlorine, bromine and iodine.

Suitable "lower alkyl" and "lower alkyl" moiety in the terms "mono(or di or tri)halo(lower)alkyl", "lower alkylamino", etc. may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl,

isopropyl, butyl, isobutyl, pentyl, hexyl and the like, in which the preferred one is C<sub>1</sub>-C<sub>4</sub> alkyl and the most preferred one is methyl, ethyl or isopropyl.

Suitable "mono(or di or tri)halo(lower)alkyl" and  
5 "mono(or di or tri)halo(lower)alkyl" moiety in the term  
"mono(or di or tri)halo(lower)alkylsulfonyl" may include  
chloromethyl, dichloromethyl, trichloromethyl, bromomethyl,  
dibromomethyl, tribromomethyl, fluoromethyl, difluoromethyl,  
trifluoromethyl, 1 or 2-chloroethyl, 1 or 2-bromoethyl, 1  
10 or 2-fluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl and  
the like.

Suitable "cyclo(lower)alkyl" and "cyclo(lower)alkyl"  
moiety in the term "cyclo(lower)alkyloxy" may include  
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the  
15 like.

Suitable "lower alkenyl" moiety in the term "lower  
alkenyloxy" may include vinyl, 1-(or 2-)propenyl, 1-(or 2-  
or 3-)butenyl, 1-(or 2- or 3- or 4-)pentenyl, 1-(or 2- or  
3- or 4- or 5-)hexenyl, methylvinyl ethylvinyl, 1-(or 2- or  
20 3-)methyl-1-(or 2-)propenyl, 1-(or 2- or 3-)ethyl-1-(or  
2-)propenyl, 1-(or 2- or 3- or 4-)methyl-1-(or 2- or 3-)-  
butenyl, and the like, in which more preferable example may  
be C<sub>2</sub>-C<sub>4</sub> alkenyl.

Suitable "lower alkoxy" and "lower alkoxy" moiety in  
25 the terms "lower alkoxycarbonyl", etc. may include methoxy,  
ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy,  
pentyloxy, t-pentyloxy, hexyloxy and the like, in which the  
preferred one is C<sub>1</sub>-C<sub>4</sub> alkoxy and the most preferred one is  
methoxy.

30 Suitable "lower alkanoyl" may include formyl, acetyl,  
propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-  
dimethylpropanoyl, hexanoyl and the like.

Suitable "leaving group" may include lower alkoxy (e.g.  
methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy,  
35 t-butoxy, pentoxy, etc.), aryloxy (e.g., phenoxy, naphthoxy,

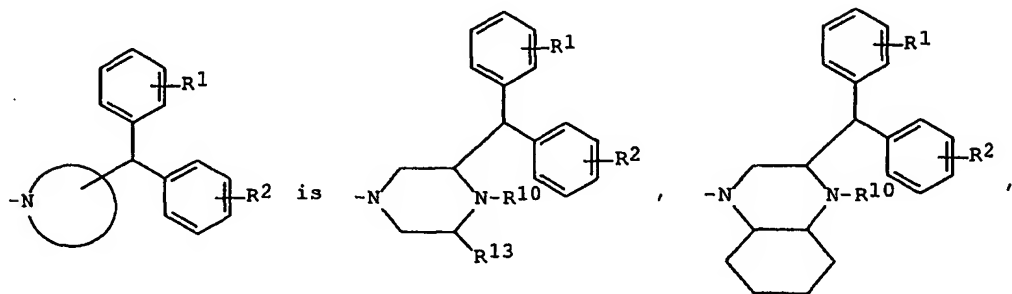
etc.), an acid residue or the like.

Suitable "acid residue" may be halogen (e.g., chlorine, bromine, iodine, etc.), sulfonyloxy (e.g., methanesulfonyloxy, phenylsulfonyloxy, mesitylenesulfonyloxy, toluenesulfonyloxy, etc.) or the like.

Preferred embodiments of the object compound (I) are as follows:

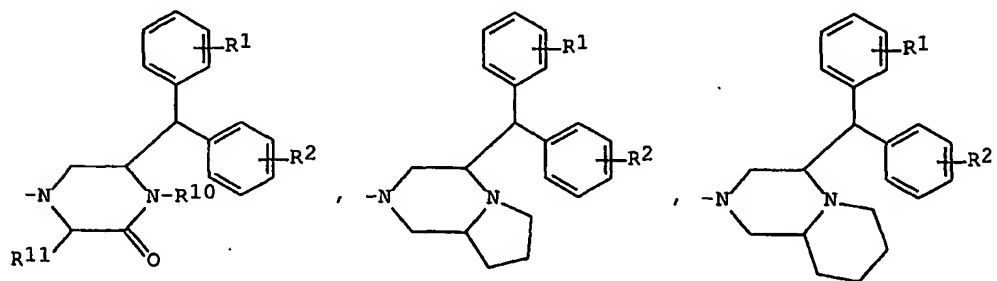
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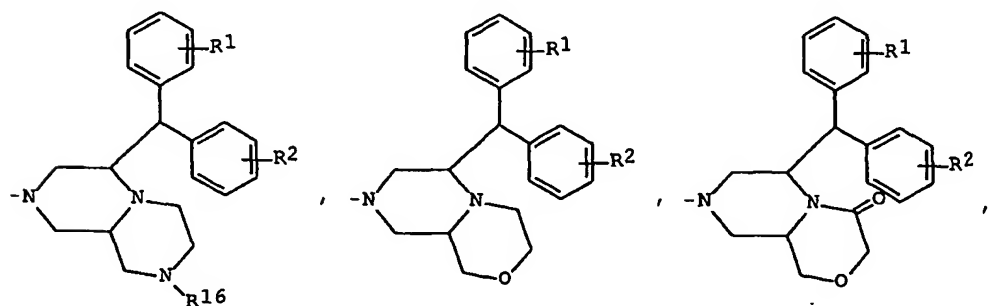
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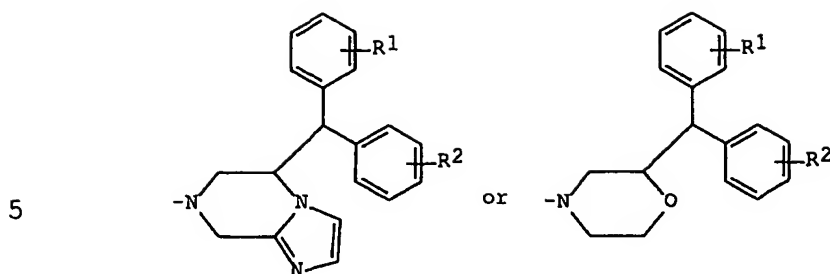
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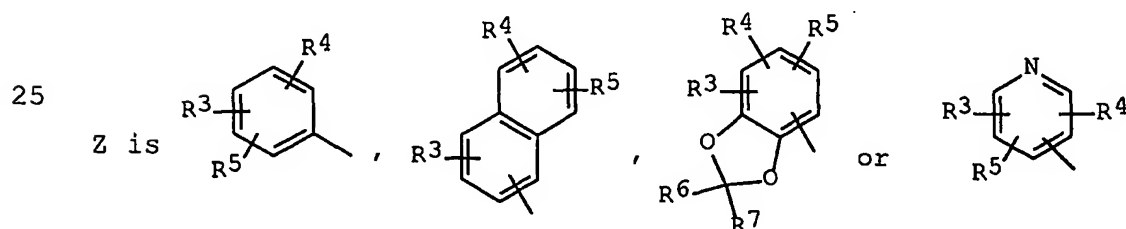
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in which R<sup>1</sup> and R<sup>2</sup> are independently hydrogen, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkyl or mono(or di or tri)halo(C<sub>1</sub>-C<sub>4</sub>)-alkyl,  
 10 R<sup>10</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl (more preferably methyl) optionally substituted with C<sub>1</sub>-C<sub>4</sub> alkoxy, carbamoyl or phenyl,  
 R<sup>11</sup> and R<sup>13</sup> are independently hydrogen, C<sub>1</sub>-C<sub>4</sub>  
 15 alkoxy carbonyl (more preferably methyl carbonyl) or C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with hydroxy or C<sub>1</sub>-C<sub>4</sub> alkoxy (more preferably hydroxymethyl),  
 R<sup>16</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl (more preferably methyl), C<sub>1</sub>-C<sub>4</sub> alkanoyl (more preferably acetyl), C<sub>1</sub>-C<sub>4</sub>  
 20 alkoxy carbonyl (more preferably methoxycarbonyl), benzyloxycarbonyl, C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl or mono(or di or tri)halo(C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl,



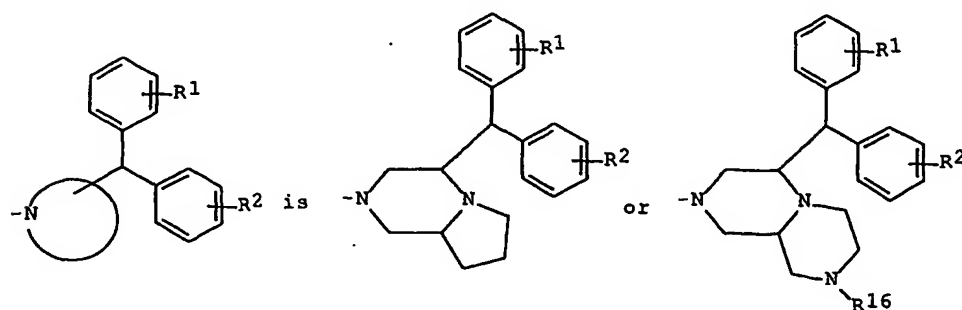
in which R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently hydrogen;  
 30 halogen (more preferably fluorine, chlorine or bromine); C<sub>1</sub>-C<sub>4</sub> alkyl (more preferably methyl); mono(or di or tri)halo(C<sub>1</sub>-C<sub>4</sub>)alkyl (more preferably trifluoromethyl); cyano; C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl (more preferably methoxycarbonyl); C<sub>1</sub>-C<sub>4</sub> alkylthio (more  
 35 preferably methylthio); C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl (more

preferably mesyl); hydroxy; C<sub>1</sub>-C<sub>4</sub> alkoxy (more preferably methoxy, ethoxy, propoxy or isopropoxy) optionally substituted with C<sub>1</sub>-C<sub>4</sub> alkoxy (more preferably methoxy), C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl (more preferably methoxycarbonyl), carbamoyl, cyano, phenyl or one, two or three halogen(s) (more preferably fluorine); C<sub>2</sub>-C<sub>4</sub> alkenyloxy (more preferably 2-propenyloxy); cyclo(C<sub>3</sub>-C<sub>6</sub>)alkyloxy (more preferably cyclopentyloxy); nitro; C<sub>1</sub>-C<sub>4</sub> alkylamino (more preferably methylamino); di(C<sub>1</sub>-C<sub>4</sub>)alkylamino (more preferably dimethylamino); or imidazolyl, pyrazolyl, thienyl, thiazolyl, furyl, tetrazolyl, pyridyl or phenyl, each of which may have a substituent selected from a group which consists of

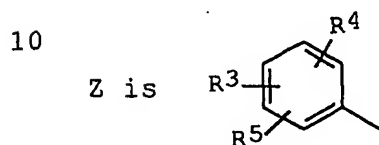
C<sub>1</sub>-C<sub>4</sub> alkyl (more preferably methyl), mono(or di or tri)halo(C<sub>1</sub>-C<sub>4</sub>)alkyl (more preferably trifluoromethyl), C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl (more preferably methylsulfonyl), C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl (more preferably methylsulfinyl), C<sub>1</sub>-C<sub>4</sub> alkylthio (more preferably methylthio), C<sub>1</sub>-C<sub>4</sub> alkylamino (more preferably methylamino) and di(C<sub>1</sub>-C<sub>4</sub>)alkylamino (more preferably dimethylamino), and

R<sup>6</sup> and R<sup>7</sup> are independently hydrogen or halogen, and R<sup>8</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl.

More preferred embodiments of the object compound (I) are as follows:



in which  $R^1$  and  $R^2$  are independently hydrogen,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkyl or mono(or di or tri)halo( $C_1$ - $C_4$ )-alkyl, and  
 $R^{16}$  is hydrogen,  $C_1$ - $C_4$  alkyl (more preferably methyl),  
 5  $C_1$ - $C_4$  alkanoyl (more preferably acetyl),  $C_1$ - $C_4$  alkoxy carbonyl (more preferably methoxy carbonyl), benzyloxy carbonyl,  $C_1$ - $C_4$  alkylsulfonyl or mono(or di or tri)halo( $C_1$ - $C_4$ )alkylsulfonyl,



in which  $R^3$  is hydrogen,  
 15  $R^4$  is  $C_1$ - $C_4$  alkoxy (more preferably methoxy), and  
 $R^5$  is imidazolyl, pyrazolyl, thienyl, thiazolyl, furyl, tetrazolyl, pyridyl or phenyl, each of which may have a substituent selected from a group which consists of  
 20  $C_1$ - $C_4$  alkyl (more preferably methyl), mono(or di or tri)halo( $C_1$ - $C_4$ )alkyl (more preferably trifluoromethyl),  $C_1$ - $C_4$  alkylsulfonyl (more preferably methylsulfonyl),  $C_1$ - $C_4$  alkylsulfinyl (more preferably methylsulfinyl),  $C_1$ - $C_4$  alkylthio (more preferably methylthio),  
 25  $C_1$ - $C_4$  alkylamino (more preferably methylamino) and di( $C_1$ - $C_4$ )alkylamino (more preferably dimethylamino), and  
 $R^8$  is hydrogen or  $C_1$ - $C_4$  alkyl.

30 The Processes 1 and 2 for preparing the object compound (I) of the present invention are explained in detail in the following.

#### Process 1

35 The object compound (I) or a salt thereof can be



prepared by reacting the compound (II) or its reactive derivative at the imino group or a salt thereof with the compound (III) or a salt thereof.

Suitable reactive derivative at the imino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (II) with phosphorus trichloride or phosgene and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g. methanol, ethanol, etc.), acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction, or the mixture thereof.

The reaction may also be carried out in the presence of a reductive reagent such as hydrides (e.g. hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, etc.), or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

#### Process 2

The object compound (Ib) or a salt thereof can be prepared by reacting the compound (Ia) or a salt thereof with the compound (IV) or a salt thereof.

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g. methanol, ethanol, etc.), acetone, dioxane, acetonitrile, chloroform,

methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvents may also be used in  
5 a mixture with water.

The reaction may also be carried out in the presence of an inorganic or organic base such as alkali metal carbonate (e.g. potassium carbonate, etc.), alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-  
10 (lower)alkyl-morpholine, N,N-di(lower)alkylethylamine (e.g. N,N-diisopropylethylamine, etc.), N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.  
15

The object compound (I) and a pharmaceutically acceptable salt thereof have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism or Neurokinin B  
20 antagonism, and therefore are useful for treating or preventing Tachykinin-mediated diseases, particularly Substance P-mediated diseases, for example, respiratory diseases such as asthma, bronchitis (e.g. chronic  
bronchitis, acute bronchitis and diffuse panbronchiolitis, etc.), rhinitis, cough, expectoration, and the like;  
25 ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like;  
cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and  
30 the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like;  
pains or aches (e.g. migraine, headache, cluster headache, toothache, cancerous pain, back pain, neuralgia, etc.); and the like.

35 Further, it is expected that the object compound (I)

and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing ophthalmic diseases such as glaucoma, uveitis, and the like;

5 gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, food allergy, and the like; inflammatory diseases such as nephritis, and the like; circulatory diseases such as hypertension, angina pectoris, cardiac failure, thrombosis, Raynaud's disease, and the  
10 like;  
epilepsy; spastic paralysis; pollakiuria; cystitis; bladder detrusor hyperreflexia; urinary incontinence; Parkinson diseases; dementia; AIDS related dementia; Alzheimer's diseases; Down's syndrome; Huntington's chorea;  
15 carcinoid syndrome; disorders related to immune enhancement or suppression; disorders caused by Helicobacter pylori or another spiral urease-positive gram-negative bacterium; sunburn; angiogenesis or diseases caused by angiogenesis; and the like.

20 It is furthermore expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing chronic obstructive pulmonary diseases, particularly chronic pulmonary emphysema; iritis; proliferative  
25 vitreoretinopathy; psoriasis; inflammatory intestinal diseases, particularly Crohn's diseases; hepatitis; superficial pain on congelation, burn, herpes zoster or diabetic neuropathy; telalgia attended to hyperlipidemia; postoperative neuroma, particularly of mastectomy; vulvar  
30 vestibulitis; hemodialysis-associated itching; lichen planus; laryngopharyngitis; bronchiectasis; coniosis; whooping cough; pulmonary tuberculosis; cystic fibrosis; emesis (e.g., nausea, retching, vomiting, acute emesis, delayed emesis, anticipatory emesis, past operative nausea  
35 and vomiting (PONV), acute and/or delayed emesis induced by

drugs such as cancer chemotherapeutic agents, etc.); mental diseases, particularly anxiety disorders, stress-related disorders, affective disorders, psychological development disorders and schizophrenia; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis; attenuation of morphine withdrawal; oedema, such as oedema caused by thermal injury; small cell carcinomas, particularly small cell lung cancer (SCLC); hypersensitivity disorders such as poison ivy; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; reflex sympathetic dystrophy such as shoulder/hand syndrome; addiction disorders such as alcoholism; stress related somatic disorders; rheumatic diseases such as fibrositis; aggressive behaviour, optionally taking an antipsychotic agent together; mania or hypomania, optionally taking an antipsychotic agent together; symptoms associated with Premenstrual Syndrome (PMS) (PMS is also now referred to as Late Luteal Phase Syndrome (LLS); psychosomatic disorders; psychoimmunologic disorders; attention deficit disorders (ADD) with or without hyperactivity; and the like.

Furthermore, the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are Central Nervous System (CNS) penetrant.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compound, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral, external including topical, enteral, intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal or transocular administration. The pharmaceutical

preparations may be solid, semi-solid or solutions such as capsules, tablets, pellets, dragees, powders, granules, suppositories, ointments, creams, lotions, inhalants, injections, cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of a patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating Tachykinin-mediated diseases such as asthma and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

In order to show the utility of the object compound (I) and a pharmaceutically acceptable salt thereof, the pharmacological test data of some representative compounds of the present invention is shown in the following.

#### Emesis in the dog

25

#### [I] Test Method

Individually housed adult female dogs (8 to 15 kg) were given an i.v. injection of a solution containing a test compound. 5 Min later the emetic responses (retching and vomiting) were induced by administration of subcutaneous apomorphine (0.1 mg/0.5 ml/kg) and observed for the next 60 min. The timing and number of retches and vomits observed were recorded for each animal. An individual animal was tested with at least 10 days between

experiments.

[II] Test Result

5       The following Test Compound showed 90% inhibition rate of emesis in the dog at the dose of 1.0 mg/kg.

Test compound:   The object compound of the  
Example 28

10       The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

      Lithium bis(trimethylsilyl)amide (1.0M in  
15 tetrahydrofuran) (77 ml) was added portionwise to a stirred solution of 1,4-dibenzyl-2,5-piperazinedione (20.6 g) in a mixture of tetrahydrofuran (400 ml) and N,N-dimethylformamide (200 ml) at 0°C. The whole was stirred at 5°C for 1 hour and thereto a solution of  
20 bromodiphenylmethane (19 g) in tetrahydrofuran (100 ml) was added at -78°C and the mixture was stirred for 2 hours at the same temperature. After being stirred at 5°C for 2 hours, the mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with 1N  
25 hydrochloric acid and brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was triturated with a mixed solvent of ethyl acetate and isopropyl alcohol, and the resulting solid was collected by filtration to give 1,4-dibenzyl-3-benzhydryl-2,5-  
30 piperazinedione (10.55 g) as a colorless powder.

      NMR (DMSO-d<sub>6</sub>, δ): 3.27 (1H, d, J=13.0Hz), 3.71 (1H, d, J=17.4Hz), 3.84 (1H, d, J=17.4Hz), 4.23 (1H, d, J=14.6Hz), 4.49-4.81 (4H, m), 7.03-7.54 (20H, m)

      MASS (APCI): 461 (M+H)<sup>+</sup>

Preparation 2

The following compound was obtained according to a similar manner to that of Example 4.

5        4-tert-Butoxycarbonyl-2-benzhydryl-1-methylpiperazine  
NMR (DMSO-d<sub>6</sub>, δ): 1.10-1.45 (9H, m), 1.21 (3H, s),  
2.40-3.50 (6H, m), 4.05-4.25 (1H, m), 7.10-7.43  
(10H, m)  
MASS (APCI): 367 (M+H)<sup>+</sup>

10

Preparation 3

4N Hydrogen chloride in 1,4-dioxane (44 ml) was added to a solution of 4-tert-butoxycarbonyl-2-benzhydryl-1-methylpiperazine (6.5 g) in ethanol (33 ml) under ice-cooling over 30 minutes. The mixture was stirred at room temperature for 4 hours and evaporated under reduced pressure. The residue was triturated with diisopropyl ether and the resulting solid was collected by filtration to give 2-benzhydrylpiperazine dihydrochloride (6.02 g) as a powder.

15  
20        NMR (DMSO-d<sub>6</sub>, δ): 2.50-3.95 (6H, m), 3.56 (3H, s),  
4.30-5.50 (2H, m), 7.21-7.57 (11H, m)  
MASS (APCI): 267 (M+H)<sup>+</sup> (free)

Preparation 4

25        A solution of 1,4-dibenzyl-3-benzhydryl-2,5-piperazinedione dihydrochloride (840 mg) in methanol (10 ml) was hydrogenated over 10% palladium-carbon (50% wet, 84 mg) at room temperature under atmospheric pressure for 5 hours. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure to give an oil, which was treated with 4N hydrogen chloride in ethyl acetate solution to give 2-benzhydrylpiperazine dihydrochloride (525 mg) as a colorless powder.

30  
35        NMR (DMSO-d<sub>6</sub>, δ): 3.12-3.89 (8H, m), 4.39 (1H, d, J=11.1Hz), 4.59 (1H, m), 7.26-7.49 (10H, m)

MASS (APCI): 253 (M+H)<sup>+</sup> (free)

#### Preparation 5

The following compounds were obtained according to a  
5 similar manner to that of Preparation 4.

(1) 6-Benzhydrylpiperazine-2-one

NMR (DMSO-d<sub>6</sub>, δ): 2.43-2.75 (3H, m), 3.19 (2H, s), 4.14  
(2H, m), 6.43 (1H, br s), 7.14-7.45 (10H, m)

10 MASS (APCI): 267 (M+H)<sup>+</sup>

(2) 5-Benzhydryl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine  
dihydrochloride

MASS (APCI): 290 (M+H)<sup>+</sup> (free)

15

(3) (2S)-2-Benzhydrylpiperazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 3.12-3.89 (8H, m), 4.39 (1H, d,  
J=11.1Hz), 4.59 (1H, m), 7.26-7.49 (10H, m)

MASS (APCI): 253 (M+H)<sup>+</sup> (free)

20

(4) (2S)-2-Benzhydryl-1-methylpiperazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.66-4.89 (12H, m), 7.21-7.56 (10H,  
m)

MASS (APCI): 267 (M+H)<sup>+</sup> (free)

25

(5) (2R)-2-Benzhydryl-1-methylpiperazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.66-4.89 (12H, m), 7.21-7.56 (10H,  
m)

MASS (APCI): 267 (M+H)<sup>+</sup> (free)

30

(6) (2R)-2-Benzhydrylpiperazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 3.12-3.89 (8H, m), 4.39 (1H, d,  
J=11.1Hz), 4.59 (1H, m), 7.26-7.49 (10H, m)

MASS (APCI): 253 (M+H)<sup>+</sup> (free)

35



Preparation 6

Di-tert-butyl carbonate (996 mg) was added to a mixture of 2-benzhydrylpiperazine dihydrochloride (1.65 g) and N,N-diisopropylethylamine (3.5 ml) in N,N-dimethylformamide (17 ml) under ice-cooling. After being stirred at same temperature for 2 hours, the mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure to give a crude oil. The oil was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (50:1) to give 1-tert-butoxycarbonyl-3-benzhydrylpiperazine (1.26 g) as a colorless powder.

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.39 (9H, s), 2.63-2.95 (4H, m), 3.34 (1H, m), 3.74-3.95 (3H, m), 7.17-7.39 (10H, m)  
MASS (APCI): 353 (M+H)<sup>+</sup>

Preparation 7

A solution of 2-benzhydryloxirane (631 mg) in isopropyl alcohol (4 ml) was added portionwise to a stirred solution of 2-aminoethyl hydrogensulfate (2.12 g) in a mixture of 20% sodium hydroxide solution (3 ml) at 50°C. The whole was stirred at 100°C for 6 hours and thereto 40% sodium hydroxide solution (6 ml) was added at 100°C. After being stirred for 18 hours at the same temperature, the mixture was partitioned between ethyl acetate and 2N sodium hydroxide. The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (20:1) to give 2-benzhydrylmorpholine (102 mg) as a colorless powder.

NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.50-2.92 (4H, m), 3.63 (1H, m), 3.84 (1H, m), 3.92 (1H, d, J=9.6Hz), 4.20 (1H, ddd, J=9.6, 9.6, 2.5Hz), 7.14-7.37 (10H, m)

MASS (APCI): 254 (M+H)<sup>+</sup>

#### Preparation 8

Lithium aluminum hydride (114 mg) was added by small portions to an ice-cooled solution of 1-benzhydryl-2-(N-methoxymethylamino)-2-oxoethylcarbamic acid tert-butyl ester (1.15 g) in tetrahydrofuran (10 ml) below 5°C under nitrogen atmosphere. After the mixture was stirred at the same temperature for 1 hour, 2N sodium hydroxide (0.5 ml) was added to the mixture. After the mixture was stirred for 30 minutes, the insoluble materials were removed by filtration and washed with tetrahydrofuran. The filtrate and the washing were combined, and evaporated under reduced pressure. The residue was dissolved into dichloromethane (15 ml), and N-benzylglycine ethyl ester (609 mg) was added to the solution. To the resulting solution sodium triacetoxymethylborohydride (1.27 g) was added portionwise under stirring and the whole was stirred at 5°C ~ room temperature overnight. The mixture was partitioned between ethyl acetate and 2N sodium hydroxide. The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated under reduced pressure to give N-benzyl-N-[2-(tert-butoxycarbonylamino)-3,3-diphenylpropyl]glycine ethyl ester (1.51 g) as a colorless oil.

MASS (APCI): 503 (M+H)<sup>+</sup>

#### Preparation 9

The following compound was obtained according to a similar manner to that of Preparation 8.

N-(2-tert-Butoxycarbonylamino-3,3-diphenylpropyl)-N-[2-methoxy-5-(trifluoromethoxy)benzyl]glycine methyl ester

NMR (CDCl<sub>3</sub>, δ): 1.32 (9H, s), 2.66 (1H, dd, J=14.5, 6.4Hz), 2.87 (1H, dd, J=13.7, 4.2Hz), 3.30 (1H, d, J=4.9Hz), 3.61 (3H, s), 3.77 (3H, s), 3.82 (2H,

m), 4.16 (1H, d, J=8.3Hz), 4.61 (1H, m), 4.86 (1H, m), 6.81 (1H, d, J=8.9Hz), 7.08-7.31 (13H, m)  
MASS (APCI): 603 (M+H)<sup>+</sup>

## 5 Preparation 10

The following compounds were obtained according to a similar manner to that of Preparation 8 followed by a similar manner to that of Preparation 13.

10 (1) 6-Benzhydryl-3-methylpiperazin-2-one hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.39 (3H, m), 2.91 (1H, m), 3.14 (1H, m), 3.52-4.46 (3H, m), 4.70 (1H, m), 7.14-7.53 (10H, m)  
MASS (APCI): 281 (M+H)<sup>+</sup> (free)

15

(2) 6-Benzhydryl-3,3-dimethylpiperazin-2-one  
NMR (CDCl<sub>3</sub>, δ): 1.35 (3H, s), 1.37 (3H, s), 2.74-2.95 (2H, m), 3.83 (1H, d, J=10.7Hz), 4.24 (1H, m), 5.57 (1H, s), 7.17-7.35 (10H, m)  
20 MASS (APCI): 295 (M+H)<sup>+</sup>

## Preparation 11

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.15 g) was added over 5 minutes to a  
25 mixture of N-(2-methoxybenzyl)glycine methyl ester hydrochloride (1.72 g), N-(tert-butoxycarbonyl)-3,3-diphenyl-L-alanine (1.71 g), 1-hydroxybenzotriazole (0.81 g) and N,N-diisopropylethylamine (1.22 ml) in dichloromethane (40 ml). After being stirred for 3 hours  
30 at room temperature, the resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of  
35 hexane and ethyl acetate (4:1) to give N-[(2S)-2-(tert-

butoxycarbonylamino)-3,3-diphenylpropionyl]-N-(2-methoxybenzyl)glycine methyl ester (2.34 g) as a colorless powder.

5 NMR (CDCl<sub>3</sub>, δ): 1.29 (9H, s), 3.62-3.77 (6H, m), 3.89 (1H, m), 4.13 (1H, m), 4.51 (2H, m), 4.86-5.07 (1H, m), 5.30-5.68 (1H, m), 6.44-7.38 (15H, m)  
MASS (APCI): 555 (M+Na)<sup>+</sup>

#### Preparation 12

10 The following compound was obtained according to a similar manner to that of Preparation 11.

N-Benzyl-N-[(2R)-2-tert-butoxycarbonylamino-3,3-diphenylpropionyl]glycine ethyl ester

15 NMR (CDCl<sub>3</sub>, δ): 1.15-1.47 (12H, m), 3.61-4.25 (4H, m), 4.48-4.76 (2H, m), 4.99-5.17 (1H, m), 5.36-5.61 (1H, m), 6.61-7.43 (15H, m)  
MASS (APCI): 417 (M+H)<sup>+</sup>

#### 20 Preparation 13

4N Hydrogen chloride in ethyl acetate solution (10 ml) was added to a solution of N-[(2S)-2-(tert-butoxycarbonylamino)-3,3-diphenylpropionyl]-N-(2-methoxybenzyl)glycine methyl ester (1.34 g) in ethyl acetate (5 ml) at room temperature. After being stirred for 2 hours, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved into isopropyl alcohol (8 ml) and the solution was stirred for 3 hours under reflux. After being cooled with ice, the residue was triturated with diisopropyl ether (50 ml) and the resulting solid was collected by filtration to give (3S)-3-benzhydryl-1-(2-methoxybenzyl)piperazine-2,5-dione (785 mg) as a colorless powder.

35 NMR (DMSO-d<sub>6</sub>, δ): 3.01 (1H, d, J=17.4Hz), 3.50 (1H, d, J=17.4Hz), 3.75 (3H, s), 4.24 (1H, d, J=15.0Hz),

4.38 (1H, d, J=15.0Hz), 4.53 (1H, d, J=5.4Hz),  
4.73 (1H, d, J=5.4Hz), 6.85-7.33 (14H, m), 8.39  
(1H, m)

MASS (APCI): 423 (M+Na)<sup>+</sup>

5

#### Preparation 14

The following compound was obtained according to a similar manner to that of Preparation 13.

10 (3R)-3-Benzhydryl-1-benzylpiperazine-2,5-dione  
NMR (DMSO-d<sub>6</sub>, δ): 2.98 (1H, d, J=17.2Hz), 3.47 (1H, d, J=17.2Hz), 4.16 (1H, d, J=14.5Hz), 4.54 (1H, d, J=5.4Hz), 4.57 (1H, d, J=14.5Hz), 4.76 (1H, dd, J=5.4, 5.4Hz), 7.07-7.41 (15H, m), 8.40 (1H, m)  
15 MASS (APCI): 371 (M+H)<sup>+</sup>

#### Preparation 15

Sodium triacetoxyborohydride (5.6 g) was added portionwise to a mixture of glycine methyl ester  
20 hydrochloride (1.63 g), N,N-diisopropylethylamine (2.27 ml) and 2-methoxy-5-(trifluoromethoxy)benzaldehyde (3.8 g) in a mixture of dichloromethane (30 ml) and acetic acid (3 drops) at 0°C and the whole was stirred at 5°C ~ room temperature overnight. The mixture was partitioned between  
25 ethyl acetate and 2N sodium hydroxide. The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (2:1).  
30 The fractions containing the objective compound were collected and evaporated under reduced pressure and treated with 4N hydrogen chloride in ethyl acetate solution to give N-[2-methoxy-5-(trifluoromethoxy)benzyl]glycine methyl ester hydrochloride (2.76 g) as a colorless powder.  
35 NMR (DMSO-d<sub>6</sub>, δ): 3.73 (3H, s), 3.86 (3H, s), 3.92 (2H,

s), 4.10 (2H, s), 7.17 (1H, d,  $J=9.1\text{Hz}$ ), 7.42 (1H, dd,  $J=9.1, 2.6\text{Hz}$ ), 7.56 (1H, d,  $J=2.6\text{Hz}$ ), 9.68 (2H, br s)

MASS (APCI): 294 (M+H)<sup>+</sup> (free)

5

#### Preparation 16

A mixture of (2S)-2-(4-methylphenylsulfonyloxymethyl)-pyrrolidine-1-carboxylic acid benzyl ester (26.2 g), 2-methoxybenzylamine (44 ml) and N,N-diisopropylethylamine (17.6 ml) in 1,3-dimethyl-2-imidazolidinone (393 ml) was stirred at 93°C for 7 hours. The mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (20:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give a syrup of (2S)-2-[(2-methoxybenzylamino)methyl]pyrrolidine-1-carboxylic acid benzyl ester (15.7 g).

10  
15  
20

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.83-2.10 (6H, m), 2.57 (1H, m), 2.81 (1H, m), 3.27-3.66 (2H, m), 3.70-4.18 (5H, m), 5.10 (2H, s), 6.82-7.78 (9H, m)

MASS (APCI): 355 (M+H)<sup>+</sup>

25

#### Preparation 17

3-Bromo-1,1-diphenyl-2-propanone (12.7 g) and N,N-diisopropylethylamine (15.7 ml) were added successively to a solution of (2S)-2-[(2-methoxybenzylamino)methyl]pyrrolidine-1-carboxylic acid benzyl ester (15.6 g) in tetrahydrofuran (156 ml) at 0°C. After being stirred at room temperature for 2 hours, the mixture was poured into ice-water (100 ml) and extracted with ethyl acetate (100 ml x 2). The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure.

30  
35

The residue was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (3:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give a colorless syrup of (2S)-2-[[N-(2-oxo-3,3-diphenylpropyl)-N-(2-methoxybenzyl)amino]methyl]pyrrolidine-1-carboxylic acid benzyl ester (1.51 g).

NMR (CDCl<sub>3</sub>, δ): 1.30-2.00 (3H, m), 2.23-2.70 (2H, m),  
3.11-3.93 (8H, m), 3.74 (3H, s), 5.06 (2H, m),  
5.36 (1H, m), 6.82-7.31 (19H, m)  
MASS (APCI): 563 (M+H)<sup>+</sup>

#### Preparation 18

(2S)-2-[[N-(2-Oxo-3,3-diphenylpropyl)-(2-methoxybenzyl)amino]methyl]pyrrolidine-1-carboxylic acid benzyl ester (492 mg) was dissolved in a mixture of methanol (7.4 ml) and 1N hydrochloric acid (0.5 ml), and the solution was hydrogenated over 10% palladium - charcoal (50% wet) (0.15 g) at room temperature under atmospheric pressure for 15 hours. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure. The residue was partitioned between aqueous saturated sodium hydrogen carbonate and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (4:1). The fractions containing the objective compound were collected and evaporated under reduced pressure and the resulting residue was treated with 4N hydrogen chloride in ethyl acetate to give (8aS)-4-benzhydryloctahydropyrrolo[1,2-a]-pyrazine dihydrochloride (221.2 mg) as a colorless solid.

NMR (CDCl<sub>3</sub>, δ): 1.29-1.37 (1H, m), 1.50-1.63 (2H, m),  
1.74-1.84 (3H, m), 2.38 (1H, ddd, J=2.2, 9.5,  
16.7Hz), 2.43 (1H, dd, J=11.0, 11.0Hz), 2.50 (1H,

dd, J=11.6, 11.0Hz), 2.66 (1H, dd, J=12.2Hz),  
2.73 (1H, dd, J=8.0, 8.5Hz), 3.12 (1H, dd,  
J=11.6, 1.8Hz), 3.33 (1H, ddd, J=8.7, 2.1,  
11.0Hz), 4.06 (1H, d, J=8.7Hz), 7.12-7.43 (10H,  
5 m)  
MASS (APCI): 293 (M+H)<sup>+</sup>

#### Preparation 19

Di-tert-butyl carbonate (3.24 g) was added to a  
10 mixture of (8aS)-4-benzhydryloctahydropyrrolo[1,2-a]-  
pyridine dihydrochloride (3.62 g) and triethylamine (3.45  
ml) in dichloromethane (100 ml) under ice-cooling. After  
being stirred at the same temperature for 3 hours, the  
reaction mixture was washed with water and brine  
15 successively, dried over magnesium sulfate and evaporated  
under reduced pressure. The residue was purified by column  
chromatography on silica gel using a mixed solvent of  
hexane and ethyl acetate (20:1). The earlier eluting  
fractions were collected and evaporated under reduced  
20 pressure to give brownish oil of (4S,8aS)-2-tert-  
butoxycarbonyl-4-benzhydryloctahydropyrrolo[1,2-a]pyridine  
(0.05 g).

NMR (CDCl<sub>3</sub>, δ): 1.38 (9H, s), 1.00-2.20 (5H, m), 2.80-  
3.00 (3H, m), 3.87 (1H, d, J=11.0Hz), 4.15 (1H,  
25 dd, J=2.4, 12.8Hz), 4.75 (1H, d, J=10.4Hz), 4.70-  
4.90 (1H, m), 5.09 (1H, dd, J=2.9, 11.2Hz), 7.05-  
7.40 (10H, m)

MASS (APCI): 393 (M+H)<sup>+</sup>, 337

30 The later eluting fractions were collected and  
evaporated under reduced pressure to give brownish oil of  
(4R,8aS)-2-tert-butoxycarbonyl-4-  
benzhydryloctahydropyrrolo[1,2-a]pyrazine (1.5 g).

NMR (CDCl<sub>3</sub>, δ): 1.38 (9H, s), 1.00-1.95 (5H, m), 2.15-  
35 2.20 (1H, m), 3.37-2.55 (2H, m), 2.70-2.75 (1H,



m), 3.10-3.20 (1H, m), 3.70-3.85 (1H, m), 4.00-4.20 (1H, m), 4.05 (1H, d, J=8.4Hz), 7.05-7.40 (10H, m)

MASS (APCI): 393 (M+H)<sup>+</sup>, 337

5

#### Preparation 20

The following compound was obtained according to a similar manner to that of Preparation 3.

10 (4R,8aS)-4-Benzhydryloctahydropyrrolo[1,2-a]pyridine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.50-5.00 (14H, m), 7.21-7.57 (10H, m), 9.50-10.20 (2H, m)

MASS (APCI): 393 (M+H)<sup>+</sup> (free)

15

#### Preparation 21

The following compound was obtained according to a similar manner to that of Example 16.

20 Methyl [2-formyl-4-[5-(trifluoromethyl)-1H-tetrazol-1-yl]phenoxy]acetate

NMR (CDCl<sub>3</sub>, δ): 3.87 (3H, s), 4.91 (2H, s), 7.10 (1H, d, J=9.0Hz), 7.66 (1H, dd, J=2.8, 9.0Hz), 8.01 (1H, d, J=2.8Hz), 10.58 (1H, s)

25 MASS (APIES negative): 329 (M-H)<sup>+</sup>

#### Preparation 22

Propyl bromide (1 ml) was added to a mixture of 2-hydroxy-6-methoxybenzaldehyde (0.45 g), potassium carbonate (0.83 g) and a small amount of potassium iodide in a mixed solvent of N,N-dimethylformamide (10 ml) and acetone (5 ml). After being stirred for 5 hours at 100°C, the mixture was poured into ice-water (20 ml) and extracted with ethyl acetate. The extract was washed with brine (10 ml), dried over magnesium sulfate and evaporated under reduced

35

pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (4:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give colorless oil of 2-methoxy-6-propoxybenzaldehyde (0.3 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.05 (3H, t, J=7.4Hz), 1.83 (2H, sext, J=7.4Hz), 3.89 (3H, s), 4.00 (2H, t, J=6.5Hz), 6.55 (2H, d, J=8.5Hz), 7.38 (1H, t, J=8.5Hz), 10.75 (1H, s)  
MASS (APCI): 195 (M+H)<sup>+</sup>

#### Preparation 23

The following compounds were obtained according to a similar manner to that of Preparation 22.

(1) 2-Methoxy-6-(2,2,2-trifluoroethoxy)benzaldehyde  
NMR (CDCl<sub>3</sub>,  $\delta$ ): 3.91 (3H, s), 4.41 (2H, q, J=8.0Hz), 6.56 (1H, d, J=8.2Hz), 6.72 (1H, d, J=8.3Hz), 7.47 (1H, t, J=8.4Hz), 10.51 (1H, s)  
MASS (APCI): 235 (M+H)<sup>+</sup>

(2) 2-Ethoxy-6-methoxybenzaldehyde  
NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.43 (3H, t, J=7.6Hz), 4.12 (2H, q, J=7.6Hz), 3.89 (3H, s), 6.53 (2H, d, J=8.5Hz), 7.38 (1H, t, J=8.5Hz), 10.53 (1H, s)  
MASS (APCI): 181 (M+H)<sup>+</sup>

#### Preparation 24

Thionyl chloride (0.58 ml) was added dropwise to a solution of L-pipecolinic acid (450 mg) in methanol at room temperature. The reaction mixture was stirred at 55°C for 2 hours. The whole mixture was evaporated under reduced pressure to give (2S)-piperidine-2-carboxylic acid methyl ester hydrochloride as a colorless oil.

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.55-1.75 (4H, m), 2.04-2.10 (1H, m),  
2.49-2.51 (1H, m), 2.91 (1H, m), 3.20-3.27 (1H,  
m), 3.77 (3H, s), 4.08 (1H, m), 9.20-9.50 (2H, m)  
MASS (APCI): 144 (M+H)<sup>+</sup> (free)

5

Preparation 25

(2S)-Piperidine-2-carboxylic acid methyl ester  
hydrochloride (625 mg) was dissolved in dichloromethane.  
Then N,N-diisopropylethylamine (0.91 ml) and benzaldehyde  
10 (0.53 ml) were added to the solution at 0°C. After the  
whole was stirred for 30 minutes at the same temperature,  
sodium triacetoxyborohydride (1.48 g) was added. The  
reaction mixture was allowed to room temperature and  
stirred for 3 hours. The mixture was poured into aqueous  
15 saturated sodium hydrogen carbonate solution and extracted  
with ethyl acetate. The extract was dried over magnesium  
sulfate and evaporated under reduced pressure to give (2S)-  
1-benzylpiperidine-2-carboxylic acid methyl ester (795 mg).

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.26-1.86 (6H, m), 2.04-2.20 (1H, m),  
20 2.88-2.99 (1H, m), 3.16 (1H, dd, J=4.9, 7.3Hz),  
3.40 (1H, d, J=13.3Hz), 3.74 (3H, s), 3.78 (1H, d,  
J=13.3Hz), 7.22-7.38 (5H, m)

MASS (APCI): 234 (M+H)<sup>+</sup>

25 Preparation 26

Lithium aluminum hydride was added to an ice-cooled  
solution of (2S)-1-benzylpiperidine-2-carboxylic acid  
methyl ester (178 mg) in tetrahydrofuran (2.7 ml) under  
nitrogen atmosphere. The mixture was stirred for 2 hours  
30 below 5°C. The reaction was quenched by a sequential  
addition of water (0.12 ml), 15% aqueous sodium hydroxide  
(0.12 ml) and water (0.36 ml) successively, and the whole  
was stirred at room temperature for 1 hour. The insoluble  
materials were removed by filtration. The filtrate was  
35 dried over sodium sulfate and evaporated under reduced

pressure to give (2S)-1-benzyl-2-(hydroxymethyl)piperidine as a colorless oil.

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.25-1.72 (6H, m), 1.97-2.19 (2H, m),  
2.43-2.49 (1H, m), 2.82-2.90 (1H, m), 3.32 (1H, d,  
5 J=13.4Hz), 3.51 (1H, dd, J=3.9, 10.8Hz), 3.87 (1H,  
dd, J=4.2, 10.8Hz), 4.06 (1H, d, J=13.4Hz), 7.20-  
7.38 (5H, m)

MASS (APCI): 206 (M+H)<sup>+</sup>

#### 10 Preparation 27

A solution of dimethyl sulfoxide (0.219 ml) in dichloromethane (1.1 ml) was added dropwise to a solution of oxalyl chloride (0.133 ml) in dichloromethane (2.7 ml) under cooling below -60°C with dry ice-acetone. After 5  
15 minutes, the mixture was allowed to -10°C, and a solution of (2S)-1-benzyl-2-(hydroxymethyl)piperidine (156.5 mg) in dichloromethane (1.6 ml) was added to the mixture. The whole mixture was then cooled below -60°C and was stirred for 20 minutes at the same temperature. After addition of  
20 triethylamine (0.64 ml) followed by stirring at room temperature, the reaction mixture was poured into water and extracted with 1,2-dichloroethane. The extract was dried over magnesium sulfate and evaporated under reduced pressure to give a syrup. Benzylamine (0.33 ml) was added  
25 to the solution of the syrup obtained above procedure in 1,2-dichloroethane (2.5 ml) with ice-cooling. After the whole was stirred for 30 minutes at the same temperature, sodium triacetoxyborohydride (0.323 g) was added to this mixture. The reaction mixture was allowed to room  
30 temperature and was stirred for 3 hours. The mixture was poured into aqueous saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The extract was dried over magnesium sulfate and evaporated under reduced pressure. The resulting residue was purified by  
35 silica gel chromatography using a mixture of

dichloromethane and methanol (20:1) as an eluent to give N-benzyl-[(2S)-1-benzylpiperidin-2-ylmethyl]amine (168.5 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.26-1.49 (3H, m), 1.56-1.67 (3H, m),  
2.03 (1H, s), 2.04-2.14 (1H, m), 2.42-2.50 (1H,  
5 m), 2.66-2.86 (3H, m), 3.25 (1H, d, J=13.6Hz),  
3.73 (2H, s), 3.92 (1H, d, J=13.6Hz), 7.19-7.38  
(20H, m)

MASS (APCI): 295 (M+H)<sup>+</sup>

#### 10 Preparation 28

The following compound was obtained according to a similar manner to that of Preparation 17.

3-[N-[(2S)-1-Benzylpiperidin-2-yl)methyl]-N-  
15 benzylamino]-1,1-diphenylpropan-2-one

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.22-1.85 (5H, m), 2.34 (1H, m), 2.61  
(2H, m), 2.88-2.95 (1H, m), 3.22 (1H, m), 3.41  
(2H, s), 3.66 (2H, s), 4.03 (1H, d, J=15.0Hz),  
4.43 (1H, d, J=5.70Hz), 5.27 (1H, s), 7.16-7.34  
20 (20H, m)

MASS (APCI): 503 (M+H)<sup>+</sup>

#### Preparation 29

25 The following compound was obtained according to a similar manner to that of Preparation 25.

(2R)-2-(Benzyloxycarbonylamino)-3-(2-methoxybenzylamino)propionic acid methyl ester

NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.90 (1H, dd, J=4.7, 12.5Hz), 3.01 (1H,  
30 dd, J=4.8, 12.5Hz), 3.73-3.89 (9H, m), 4.40 (1H,  
m), 5.82 (1H, br), 6.83-7.55 (9H, m)

MASS (APCI): 373 (M+H)<sup>+</sup>

#### Preparation 30

35 The following compounds were obtained according to a

similar manner to that of Preparation 17.

- (1) (2R)-2-(Benzyloxycarbonylamino)-3-[N-(2-methoxybenzyl)-N-(2-oxo-3,3-diphenylpropyl)amino]-propionic acid methyl ester  
5 NMR (CDCl<sub>3</sub>,  $\delta$ ): 3.08 (2H, d, J=5.6Hz), 3.42 (2H, s), 3.60 (2H, s), 3.70 (3H, s), 3.75 (3H, s), 3.77 (1H, m), 4.26 (1H, m), 5.00 (1H, s), 5.12 (1H, s), 6.41 (1H, d, J=7.0Hz), 6.72-7.34 (19H, m)  
10 MASS (ESI): 581 (M+H)<sup>+</sup>, 603 (M+Na)<sup>+</sup>
- (2) 3-[N-Benzyl-N-[(4-benzylmorpholin-3-yl)methyl]amino]-1,1-diphenylpropan-2-one  
IR (Neat): 1724 cm<sup>-1</sup>  
15 NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.05-2.17 (1H, m), 2.40-2.70 (3H, m), 2.98 (1H, dd, J=3.6, 13.2Hz), 3.13 (1H, d, J=13.4Hz), 3.51 (2H, s), 3.67 (2H, s), 3.41-3.65 (1H, m), 3.86 (1H, dd, J=3.0, 11.2Hz), 4.04 (1H, d, J=13.4Hz), 5.10 (1H, s), 7.14-7.34 (20H, m)  
20 MASS (APCI): 504 (M+H)<sup>+</sup>

#### Preparation 31

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimido hydrochloride (5.74 g) was added to a solution of (3S)-4-benzyl-5-oxomorpholine-3-carboxylic acid (10.0 g),  
25 benzylamine (4.65 ml), 1-hydroxybenzotriazole (5.74 g) and triethylamine (8.89 ml) in dichloromethane (100 ml) under ice-cooling. After being stirred for 15 hours at room temperature, the reaction mixture was washed with aqueous sodium carbonate, 1N hydrochloric acid and brine  
30 successively, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of toluene and ethyl acetate (4:1). The fractions containing  
35 the objective compound were collected and evaporated under

reduced pressure to give colorless oil of N-benzyl((3S)-4-benzyl-5-oxomorpholin-3-yl)amide (11.6 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 3.72 (1H, dd, J=3.9, 12.0Hz), 3.79 (1H, d, J=14.6Hz), 3.70-3.85 (1H, m), 4.18 (2H, q, J=17.0Hz), 4.27-4.35 (1H, m), 4.37 (1H, dd, J=5.6, 14.8Hz), 4.56 (1H, dd, J=5.6, 14.8Hz), 5.46 (1H, d, J=14.6Hz), 6.80-6.90 (1H, m), 7.20-7.50 (10H, m)

MASS (APCI): 325 (M+H)<sup>+</sup>

### Preparation 32

Lithium aluminum hydride (4.7 g) was added by small portions to a solution of N-benzyl((3S)-4-benzyl-5-oxomorpholin-3-yl)amide (8.0 g) in tetrahydrofuran (50 ml) under nitrogen atmosphere, and the whole was stirred at 70°C for 15 hours. After being cooled with ice, 2N sodium hydroxide (2 ml) was added to the mixture under nitrogen atmosphere. The resulting precipitates were filtered off and washed with tetrahydrofuran, and the filtrate and the washings were combined and evaporated under reduced pressure to give a crude oil. The oil was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (9:1). The fractions containing the objective compound were collected, evaporated under reduced pressure to give an oil of N-benzyl[(4-benzylmorpholin-3-yl)methyl]amine (2.4 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.18-2.29 (1H, m), 2.50-2.92 (4H, m), 3.17 (1H, d, J=13.4Hz), 3.51-3.86 (7H, m), 3.99 (1H, d, J=13.4Hz), 7.21-7.31 (10H, m)

MASS (APCI): 297 (M+H)<sup>+</sup>

### Preparation 33

The following compound was obtained according to a similar manner to that of Preparation 18.

(6R, 9aR)-6-Benzhydryl-8-tert-butoxycarbonyl-octahydropyrazino[2,1-c][1,4]oxazine

IR (Nujol): 3400, 1715, 1605, 1530, 1500, 1450, 1240, 1200, 1120  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.33 (9H, s), 2.00-3.72 (12H, m), 4.18 (1H, d,  $J=7.4\text{Hz}$ ), 7.16-7.31 (10H, m)

MASS (APCI): 409 ( $\text{M}+\text{H}$ )<sup>+</sup>

#### Preparation 34

10 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.11 g) was added over 5 minutes to a mixture of N,O-dimethylhydroxylamine hydrochloride (1.17 g), (2S)-piperazine-1,2,4-tricarboxylic acid 4-benzyl ester 1-tert-butyl ester (3.64 g), 1-hydroxybenzotriazole (1.49 g)  
15 and N,N-diisopropylethylamine (2.1 ml) in dichloromethane (40 ml). After being stirred for 18 hours at room temperature, the resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The  
20 residue was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (3:1) to give 2-(N-methoxy-N-methylcarbamoyl)piperazine-1,4-dicarboxylic acid 4-benzyl ester 1-tert-butyl ester (3.61 g) as a colorless powder.

25 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.45 (9H, s), 2.90-3.20 (5H, m), 3.60-4.20 (6H, m), 4.41 (1H, m), 4.90 (1H, m), 5.06 (1H, d,  $J=12.4\text{Hz}$ ), 5.16 (1H, d,  $J=12.4\text{Hz}$ ), 7.33 (5H, m)

MASS (APCI): 308 ( $\text{M}-\text{Boc}+\text{H}$ )<sup>+</sup>

30

#### Preparation 35

Lithium aluminum hydride (38 mg) was added by small portions to an ice-cooled solution of 2-(N-methoxy-N-methylcarbamoyl)piperazine-1,4-dicarboxylic acid 4-benzyl  
35 ester 1-tert-butyl ester (407 mg) in tetrahydrofuran (5 ml)



below 5°C under nitrogen atmosphere. After the mixture was stirred at the same temperature for 2.5 hours, 2N sodium hydroxide (0.2 ml) was added to the mixture. After the mixture was stirred for 30 minutes, the insoluble materials were removed by filtration and washed with tetrahydrofuran. The filtrate and the washing were combined, and evaporated under reduced pressure to give a residue. Sodium triacetoxymethylborohydride (424 mg) was added portionwisely to a stirred mixture of the residue obtained in the above procedure and 2-methoxybenzylamine (151 mg) in dichloromethane (4 ml). After being stirred at room temperature for 4 hours, 3-bromo-1,1-diphenyl-2-propanone (347 mg) in N,N-dimethylformamide (5 ml) and N,N-diisopropylethylamine (0.35 ml) were added successively to the reaction mixture at 5°C. The whole mixture was stirred at room temperature for 36 hours and then poured into ice-water, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (4:1) to give (2R)-2-[[N-(2-methoxybenzyl)-N-(2-oxo-3,3-diphenylpropyl)-amino]methyl]piperazine-1,4-dicarboxylic acid 4-benzyl ester 1-tert-butyl ester (170 mg) as a colorless powder.

NMR (CDCl<sub>3</sub>, δ): 1.41-1.57 (9H, m), 2.70-3.00 (5H, m), 3.25-4.35 (11H, m), 4.95-5.15 (3H, m), 6.70-7.29 (19H, m)

#### Preparation 36

To a solution of (1RS,2RS)-1,2-cyclohexanediamine (114 mg) in N,N-dimethylformamide (4 ml) were added 3-bromo-1,1-diphenyl-2-propanone (289 mg) and sodium triacetoxymethylborohydride (268 mg) successively and the mixture was stirred at ambient temperature for 5 hours. The reaction mixture was diluted with water (20 ml) and

extracted with ethyl acetate three times. After the combined extract was washed with water, the organic phase was extracted with 1N hydrochloric acid. The aqueous phase was adjusted to pH 9-10 with sodium hydroxide under ice-cooling and then extracted with ethyl acetate three times. The combined extract was washed with water and brine successively, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in tetrahydrofuran (5 ml) and to the solution were added triethylamine (404 mg) and di-tert-butyl dicarbonate (436 mg) successively. After the mixture was stirred at ambient temperature for 3 hours, the volatile materials were removed under reduced pressure. The residue was purified by silica gel column chromatography eluted with a mixture of ethyl acetate and hexane (1:3) to give 161 mg of tert-butyl (3RS,4aSR,8aSR)-3-benzhydryloctahydroquinoxaline-1-carboxylate as a mixture with some impurities. Purification of this product by preparative thin layer chromatography (40% ethyl acetate in hexane) gave tert-butyl (3RS,4aSR,8aSR)-3-benzhydryloctahydroquinoxaline-1-carboxylate (42.3 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.12-1.90 (8H, m), 1.36 (9H, s), 2.34 (1H, br d, J=12.8Hz), 2.57-2.67 (1H, m), 2.80-2.95 (2H, m), 3.57-3.83 (3H, m), 7.16-7.38 (10H, m)

MASS (APCI): 407 (M+H)<sup>+</sup>

#### Preparation 37

tert-Butyl (3RS,4aSR,8aSR)-3-benzhydryloctahydroquinoxaline-1-carboxylate (42 mg) was dissolved in 4N ethyl acetate solution of hydrogen chloride (4 ml) and the mixture was stirred at ambient temperature for 3 hours. The volatile materials were removed under reduced pressure to give (2RS,4aSR,8aSR)-2-benzhydryldecahydroquinoxaline dihydrochloride (28 mg).

NMR (CDCl<sub>3</sub>, δ): 1.20-2.15 (8H, m), 3.39-3.66 (8H, m),  
4.88 (1H, d, J=11.2Hz), 7.26-7.59 (10H, m)  
MASS (APCI): 307 (M+H)<sup>+</sup> (free)

5 Preparation 38

The following compound was obtained according to a similar manner to that of Preparation 36.

tert-Butyl (3RS,4aSR,8aRS)-3-  
10 benzhydryloctahydroquinoxaline-1-carboxylate  
NMR (CDCl<sub>3</sub>, δ): 1.11-2.12 (9H, m), 1.34 (9H, s), 3.13-  
3.28 (2H, m), 3.36-3.81 (2H, m), 4.02-4.14 (1H,  
m), 4.49 (1H, d, J=11.5Hz), 7.06-7.40 (10H, m)  
MASS (APCI): 407 (M+H)<sup>+</sup>

15

Preparation 39

tert-Butyl (3RS,4aSR,8aRS)-3-  
benzhydryloctahydroquinoxaline-1-carboxylate (100 mg) was  
dissolved in hydrogen chloride (5 ml, 4N solution in ethyl  
20 acetate) and the mixture was stirred at ambient temperature  
for 3 hours. The volatile materials were removed under  
reduced pressure to give (2RS,4aRS,8aSR)-2-  
benzhydryldecahydroquinoxaline dihydrochloride, which was  
dissolved in water and washed with ethyl acetate. The  
25 aqueous phase was adjusted to pH 9-10 and extracted with  
ethyl acetate three times. The combined extract was washed  
with brine, dried over magnesium sulfate, and concentrated  
in vacuo to give (2RS,4aRS,8aSR)-2-  
benzhydryldecahydroquinoxaline (88 mg).

30 NMR (CDCl<sub>3</sub>, δ): 1.19-1.83 (9H, m), 2.19-2.36 (1H, m),  
2.51 (1H, dd, J=11.4 and 9.4Hz), 2.73-2.87 (2H,  
m), 3.07 (1H, d, J=2.9Hz), 3.63-3.82 (2H, m),  
7.10-7.42 (10H, m)  
MASS (APCI): 307 (M+H)<sup>+</sup>

35

Preparation 40

The following compound was obtained according to a similar manner to that of Example 14 from 3-formyl-4-methoxyphenylboronic acid.

5

## 2-Methoxy-5-(4-pyridyl)benzaldehyde

NMR (CDCl<sub>3</sub>,  $\delta$ ): 4.00 (3H, s), 7.12 (1H, m), 7.45-7.53 (2H, m), 7.85 (1H, dd, J=2.5, 8.7Hz), 8.14 (1H, m), 8.64-8.97 (2H, m), 10.52 (1H, s)

10

MASS (APCI): 214 (M+H)<sup>+</sup>Preparation 41

The following compounds were obtained according to a similar manner to that of Preparation 22 from each corresponding hydroxybenzaldehyde.

15

## (1) 2-Ethoxy-4,6-dimethoxybenzaldehyde

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.46 (3H, t, J=7.0Hz), 3.86 (3H, s), 3.88 (3H, s), 4.09 (2H, q, J=7.0Hz), 6.07 (2H, s), 10.38 (1H, s)

20

MASS (APCI): 211 (M+H)<sup>+</sup>

## (2) 2-Isopropoxy-4,6-dimethoxybenzaldehyde

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.38 (6H, d, J=6.1Hz), 3.86 (3H, s), 3.88 (3H, s), 4.59 (1H, m), 6.06 (1H, d, J=2.1Hz), 6.08 (1H, d, J=2.1Hz), 10.36 (1H, s)

25

MASS (ESI): 247 (M+Na)<sup>+</sup>

## (3) 5-(1H-Imidazol-1-yl)-2-methoxybenzaldehyde

NMR (CDCl<sub>3</sub>,  $\delta$ ): 4.00 (3H, s), 7.06-7.85 (6H, m), 10.50 (1H, s)

30

MASS (APCI): 203 (M+H)<sup>+</sup>Preparation 42

35

The following compound was obtained according to a

similar manner to that of Preparation 27.

Benzyl (2S)-2-[(benzylamino)methyl]-1-pyrrolidinecarboxylate

5 IR (neat, FT-IR): 3410, 2765, 1695, 1420, 1355  $\text{cm}^{-1}$   
NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ): 1.69-2.12 (4H, m), 3.20 (2H, br s),  
4.04-4.26 (3H, m), 5.01-5.16 (2H, m), 7.26-7.53  
(10H, m)  
MASS (APCI): 325 (M+H)<sup>+</sup>

10

#### Preparation 43

The following compound was obtained according to a similar manner to that of Preparation 17.

15 Benzyl (2S)-2-[[benzyl[3,3-bis(4-fluorophenyl)-2-oxopropyl]amino]methyl]-1-pyrrolidinecarboxylate  
IR (neat, FT-IR): 1700, 1415, 1335  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.48-5.30 (16H, m), 6.91-7.33 (18H, m)  
MASS (APCI): 569 (M+H)<sup>+</sup>

20

#### Preparation 44

The following compound was obtained according to a similar manner to that of Preparation 18.

25 (4R,8aS)-4-[Bis(4-fluorophenyl)methyl]-octahydropyrrolo[1,2-a]pyrazine

#### Preparation 45

30 The following compound was obtained according to a similar manner to that of Preparation 34.

Benzyl (2S)-2-(N-methoxy-N-methylcarbamoyl)-1-pyrrolidinecarboxylate

35 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.82-2.26 (4H, m), 3.10-3.22 (3H, m),  
3.49-3.72 (2H, m), 3.41-3.80 (3H, m), 4.63-4.81

(1H, m), 5.00-5.23 (2H, m), 7.27-7.38 (5H, m)  
MASS (APCI): 293 (M+H)<sup>+</sup>

#### Preparation 46

5 Methyl magnesium bromide in tetrahydrofuran (1M, 36.9 ml) was added into a solution of benzyl (2S)-2-(N-methoxy-N-methylcarbamoyl)-1-pyrrolidinecarboxylate (3.6 g) in tetrahydrofuran (36 ml) under ice-cooling. After being stirred for 2 hours at the same temperature, the reaction  
10 mixture was poured into saturated aqueous ammonium chloride, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography with a mixture of  
15 hexane and ethyl acetate (1:1) as an eluent to give benzyl (2S)-2-acetyl-1-pyrrolidinecarboxylate (0.81 g).

NMR (CDCl<sub>3</sub>, δ): 1.71-2.27 (7H, m), 3.51-3.63 (2H, m),  
4.28-4.45 (1H, ddd, J=4.6, 8.4, 13Hz), 5.02-5.21  
(2H, m), 7.26-7.36 (5H, m)  
20 MASS (APCI): 248 (M+H)<sup>+</sup>

#### Preparation 47

The following compound was obtained according to a similar manner for Preparation 25 from benzyl (2S)-2-acetyl-1-pyrrolidinecarboxylate.  
25

Benzyl (2S)-2-[1-(benzylamino)ethyl]-1-pyrrolidinecarboxylate

NMR (CDCl<sub>3</sub>, δ): 1.01-2.04 (8H, m), 2.99-4.45 (6H, m),  
30 5.10 (2H, br), 7.21-7.32 (10H, m)  
MASS (APCI): 339 (M+H)<sup>+</sup>

#### Preparation 48

The following compound was obtained according to a similar manner to that of Preparation 17 from benzyl (2S)-  
35

2-[1-(benzylamino)ethyl]-1-pyrrolidinecarboxylate.

Benzyl (2S)-2-[1-[N-benzyl-N-(2-oxo-3,3-diphenylpropyl)amino]ethyl]-1-pyrrolidinecarboxylate

5 NMR (CDCl<sub>3</sub>, δ): 0.81-5.24 (23H, m), 7.13-7.79 (15H, m)  
MASS (APCI): 547 (M+H)<sup>+</sup>

#### Preparation 49

Benzyl (2S)-2-[1-[N-benzyl-N-(2-oxo-3,3-diphenylpropyl)amino]ethyl]-1-pyrrolidinecarboxylate was  
10 dissolved in a mixture of methanol (4 ml), tetrahydrofuran  
(0.5 ml) and 1N-hydrochloric acid (0.41 ml). The solution  
was hydrogenated over 10% palladium-charcoal (50% wet) at  
room temperature under 3 atom pressure for 5 hours. After  
15 removal of the catalyst by filtration, the filtrate was  
evaporated under reduced pressure. The residue was  
partitioned between aqueous saturated sodium hydrogen  
carbonate and ethyl acetate. The organic layer was washed  
with brine, dried over magnesium sulfate and evaporated  
20 under reduced pressure. The residue was purified by silica  
gel column chromatography with a mixture of dichloromethane  
and methanol (6:1) as an eluent. The earlier and later  
fractions were separately collected and evaporated under  
reduced pressure separately to give each colorless oil,  
25 which were used for next steps separately.

The later eluting fractions of (1R or 1S,4R,8aS)-4-benzhydryl-1-methyloctahydropyrrolo[1,2-a]pyrazine

30 NMR (CDCl<sub>3</sub>, δ): 1.04-4.10 (16H, m), 6.90-7.42 (10H, m)  
MASS (APCI): 307 (M+H)<sup>+</sup>

The earlier eluting fractions of (1S or 1R,4R,8aS)-4-benzhydryl-1-methyloctahydropyrrolo[1,2-a]pyrazine

35 NMR (CDCl<sub>3</sub>, δ): 1.04-2.82 (12H, m), 3.44-4.17 (4H, m),  
6.90-7.42 (10H, m)

MASS (APCI): 307 (M+H)<sup>+</sup>

#### Preparation 50

The following compound was obtained according to a similar manner to that of Preparation 27.

Benzyl (2S,4R)-2-[(benzylamino)methyl]-4-[[tert-butyl(dimethyl)silyl]oxy]-1-pyrrolidinecarboxylate

IR (Neat): 1702, 1422, 1504 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ): 0.89 (9H, s), 0.13 (6H, s), 1.90-2.00 (2H, m), 2.70-2.85 (2H, m), 3.40-3.50 (2H, m), 3.70-3.85 (2H, m), 4.11 (1H, br s), 4.35-4.45 (1H, m), 5.05-5.20 (2H, m), 7.16-7.35 (10H, m)

MASS (APCI): 455 (M+H)<sup>+</sup> (free)

#### Preparation 51

The following compound was obtained according to a similar manner to that of Preparation 17.

Benzyl (2S,4R)-2-[[N-benzyl-N-(2-oxo-3,3-diphenylpropyl)amino]methyl]-4-[[tert-butyl(dimethyl)silyl]oxy]-1-pyrrolidinecarboxylate

NMR (CDCl<sub>3</sub>, δ): 0.13 (6H, s), 0.82 (9H, s), 1.60-4.20 (12H, m), 5.00-5.20 (3H, m), 7.16-7.35 (20H, m)

MASS (APCI): 685 (M+Na), 663 (M+H)<sup>+</sup>, 505, 455, 415, 356

#### Preparation 52

A solution of (2S,4R)-2-[[N-benzyl-N-(2-oxo-3,3-diphenylpropyl)amino]methyl]-4-[(tert-

butyldimethylsilyl)oxy]-1-pyrrolidinecarboxylate (4.82 g) and acetic acid (0.87 g) in methanol (100 ml) was

hydrogenated over 10% palladium-charcoal (50% wet, 1.0 g) at room temperature under 2-3 atoms for 15 hours. After removal of the catalyst by filtration, the filtrate was

evaporated under reduced pressure to give bis(acetic acid)



salt of (7R,8aS)-4-benzhydryl-7-[(tert-butyl)dimethylsilyl]oxy]octahydropyrrolo[1,2-a]pyrazine (4.05 g) as a syrup.

IR (KBr): 3400, 1648, 1504  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): -0.20 - -0.11 (6H, m), 0.74-0.81 (9H, m), 2.03 (6H, s), 1.60-1.80 (2H, m), 2.00-4.70 (10H, m), 7.16-7.35 (10H, m)

MASS (APCI): 423 (M+H)<sup>+</sup> (free)

#### 10 Preparation 53

Di-tert-butyl dicarbonate (4.4 g) was added to an ice-cooled mixture of bis(acetic acid) salt of (7R,8aS)-4-benzhydryl-7-[(tert-butyl)dimethylsilyl]oxy]octahydropyrrolo[1,2-a]pyrazine (7.6 g) and triethylamine (4.9 ml) in dichloromethane (200 ml). After being stirred at the same temperature for 3 hours the reaction mixture was washed with water and brine successively, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (4:1). The eluting fractions were collected and evaporated under reduced pressure to give colorless oil of tert-butyl (7R,8aS)-4-benzhydryl-7-[(tert-butyl)dimethylsilyl]oxy]hexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (6.9 g). 20

25 This compound (6.88 g) was dissolved into 1M tetrabutylammonium fluoride in tetrahydrofuran (65 ml). After being stirred for 3 hours at room temperature the reaction mixture was poured into water, the whole was extracted with ethyl acetate. The extract was washed with 30 brine, dried over magnesium sulfate and evaporated under reduced pressure. The syrup was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (4:1). The later eluting fractions were collected and evaporated under reduced 35 pressure to give colorless oil of tert-butyl (4R,7R,8aS)-4-

benzhydryl-7-hydroxyhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (1.3 g).

IR (neat): 1695, 1504  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.43 (9H, s), 1.31-1.74 (3H, m), 2.20-2.75 (3H, m), 1.93 (1H, dd,  $J=4.2$  and  $9.9\text{Hz}$ ), 3.08 (1H, dd,  $J=6.1$  and  $9.9\text{Hz}$ ), 3.30-3.40 (1H, m), 3.60-3.70 (1H, m), 3.78 (1H, br s), 3.94 (1H, d,  $J=9.0\text{Hz}$ ), 4.15-4.19 (1H, m), 7.13-7.45 (10H, m)

10 MASS (APCI): 409 ( $\text{M}+\text{H}$ )<sup>+</sup> (free)

The earlier eluting fractions were collected and evaporated under reduced pressure to give colorless oil of tert-butyl (4S,7R,8aS)-4-benzhydryl-7-hydroxyhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate

15 (1.5 g).

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.32 (9H, s), 1.50-2.00 (3H, m), 2.40-2.55 (2H, m), 3.00-3.10 (2H, m), 3.40-4.05 (5H, m), 4.30 (1H, d,  $J=11.2\text{Hz}$ ), 7.15-7.45 (10H, m)

20 MASS (APCI): 409 ( $\text{M}+\text{H}$ )<sup>+</sup> (free)

#### Preparation 54

Methyl iodide (23  $\mu\text{l}$ ) was added to an ice-cooled mixture of tert-butyl (4S,7R,8aS)-4-benzhydryl-7-hydroxyhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate

25 (155 mg) and cetyltrimethylammonium bromide (15 mg) and finely powdered sodium hydroxide (76 mg) in dichloromethane (2 ml), and the whole was stirred for 5 hours. Additional methyl iodide (23  $\mu\text{l}$ ) was added to the mixture and the mixture was further stirred overnight. The resulting

30 mixture was poured into water and extracted with dichloromethane. The organic layer was separated, dried over magnesium sulfate, concentrated under reduced pressure. The syrup was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (4:1).

35 The fractions containing the objective compound were

collected to give tert-butyl (4S,7R,8aS)-4-benzhydryl-7-methoxyhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (56 mg) as a syrup.

IR (neat): 3400, 1691, 1504  $\text{cm}^{-1}$

5        MASS (APCI): 423 (M+H)<sup>+</sup>

#### Preparation 55

The following compound was obtained according to a similar manners to that of Preparations 54 and 37.

10

(4R,7R,8aS)-4-Benzhydryl-7-methoxyoctahydropyrrolo[1,2-a]pyrazine dihydrochloride

MASS (APCI): 323 (M+H)<sup>+</sup>

#### 15    Preparation 56

Methanesulfonyl chloride (0.18 ml) was added dropwise to an ice-cooled solution of tert-butyl (4R,7R,8aS)-4-benzhydryl-7-hydroxyhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (0.78 g) and triethylamine (0.53 ml) in  
20    dichloromethane. After being stirred for 3 hours at the same temperature the mixture was washed with aqueous saturated sodium hydrogen carbonate, dried over magnesium sulfate and concentrated under reduced pressure. The syrup obtained by above procedure and sodium azide (126 mg) was  
25    dissolved into dimethylsulfoxide (5 ml). The whole was stirred at 75°C for 15 hours. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The syrup was  
30    purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (30:1). The fractions containing the objective compound were collected to give (4R,7S,8aS)-4-benzhydryl-2-(tert-butoxycarbonyl)octahydropyrrolo[1,2-a]pyrazine-7-azide  
35    (0.70 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.30-1.40 (2H, m), 1.38 (9H, s), 1.98-  
2.06 (1H, m), 2.15-2.27 (2H, m), 2.31-2.65 (2H,  
m), 2.78 (1H, d, J=8.6Hz), 3.00-3.20 (1H, m),  
3.63-3.72 (2H, m), 4.04 (1H, d, J=8.7Hz), 7.13-  
5 7.43 (10H, m)  
MASS (APCI): 434 (M+H)<sup>+</sup> (free)

#### Preparation 57

10 10% Palladium-charcoal (50% wet, 40 mg) and 0.1N  
hydrochloric acid (0.1 ml) were added into a solution of  
tert-butyl (4R,7R,8aS)-7-azido-4-  
benzhydrylhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate  
(200 mg) in methanol (2.5 ml) at room temperature. The  
mixture was hydrogenated at room temperature under  
15 atmospheric pressure for 4 hours. The palladium was  
filtered and washed with methanol. The filtrate and  
washings were combined and concentrated in vacuo. The  
resulting residue was partitioned between aqueous sodium  
hydrogen carbonate and ethyl acetate. The organic layer  
20 was separated, dried over magnesium sulfate and evaporated  
under reduced pressure. The resulting residue was purified  
by silica gel column chromatography with a mixture of  
dichloromethane and methanol (15:1) as an eluent. The  
fractions containing the objective compound were collected  
25 to give tert-butyl (4R,7R,8aS)-7-amino-4-  
benzhydrylhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate  
(193 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.22-1.65 (15H, m), 2.30-2.51 (3H, m),  
3.00-3.40 (2H, m), 3.68-4.10 (3H, m), 7.13-7.42  
30 (10H, m)  
MASS (APCI): 408 (M+H)<sup>+</sup>

#### Preparation 58

The following compound was obtained according to a  
35 similar manner to that of Preparation 57.

tert-Butyl (4R,7S,8aS)-7-amino-4-benzhydrylhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate

IR (KBr): 3300-3100, 1697  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.00-1.10 (1H, m), 1.38 (9H, s), 1.80-3.80 (10H, m), 4.07 (1H, d,  $J=8.0\text{Hz}$ ), 7.13-7.40 (10H, m)

MASS (APCI): 408 (M+H)<sup>+</sup>

10 Preparation 59

Sodium triacetoxymethylborohydride (241 mg) was added to an ice-cooled solution of tert-butyl (4R,7S,8aS)-7-amino-4-benzhydrylhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (0.23 g) and aqueous 30% formaldehyde (0.17 ml) in 15 dichloromethane (10 ml). After being stirred for 15 hours at room temperature the mixture was washed with aqueous saturated sodium hydrogen carbonate, dried over magnesium sulfate and concentrated under reduced pressure. The syrup was purified by column chromatography on silica gel using a 20 mixed solvent of dichloromethane and methanol (40:1). The fractions containing the objective compound were collected to give tert-butyl (4R,7S,8aS)-4-benzhydryl-7-(dimethylamino)hexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (210 mg).

25 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.20-1.40 (1H, m), 1.37 (9H, s), 1.90-4.20 (10H, m), 2.06 (6H, s), 4.06 (1H, d,  $J=8.0\text{Hz}$ ), 7.13-7.41 (10H, m)

MASS (APCI): 436 (M+H)<sup>+</sup>

30 Preparation 60

The following compound was obtained according to a similar manner to that of Preparation 3.

35 N-[(4R,7S,8aS)-4-Benzhydryloctahydropyrrolo[1,2-a]pyrazin]-7-N,N-dimethylamine trihydrochloride

IR (KBr): 3400, 1648, 1504  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 1.50-4.10 (15H, m), 4.26 (1H, d,  $J=9.0\text{Hz}$ ), 7.20-7.43 (10H, m), 9.20-9.60 (3H, m), 10.91 (1H, br s)

5 MASS (APCI): 336  $(\text{M}+\text{H})^+$  (free)

#### Preparation 61

A solution of benzyl chloroformate (58  $\mu\text{l}$ ) in dichloromethane (0.5 ml) was added dropwise to an ice-cooled solution of tert-butyl (4R,7S,8aS)-7-amino-4-benzhydrylhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate and triethylamine (96  $\mu\text{l}$ ) in dichloromethane (2 ml), and the whole was stirred for 2 hours at the same temperature. The mixture was poured into water and extracted with dichloromethane. The organic layer was separated, dried over magnesium sulfate and concentrated under reduced pressure. The syrup was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (4:1). The fractions containing the objective compound were collected to give tert-butyl (4R,7S,8aS)-4-benzhydryl-7-[(benzyloxycarbonyl)amino]hexahydropyrrolo-[1,2-a]pyrazine-2(1H)-carboxylate (190 mg) as a syrup.

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.00-1.20 (1H, m), 1.37 (9H, s), 2.00-2.70 (6H, m), 3.00-3.10 (1H, m), 3.70-4.20 (3H, m), 4.02 (1H, d,  $J=8.0\text{Hz}$ ), 4.98 (1H, d,  $J=8.6\text{Hz}$ ), 5.06 (2H, s), 7.13-7.40 (15H, m)

25 MASS (APCI): 542  $(\text{M}+\text{H})^+$

#### Preparation 62

30 The following compound was obtained according to a similar manner to that of preparation 3.

Benzyl (4R,7S,8aS)-4-benzhydryloctahydropyrrolo[1,2-a]pyrazin-7-ylcarbamate dihydrochloride

35 NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 1.40-5.10 (15H, m), 4.60 (2H, s), 7.16-

7.80 (13H, m), 8.21 (1H, br s)  
MASS (APCI): 442 (M+H)<sup>+</sup> (free)

#### Preparation 63

5 (Dimethylamino)sulfur trifluoride (0.068 ml) was added dropwise to a solution of tert-butyl (4R,7R,8aS)-4-benzhydryl-7-hydroxyhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (115 mg) in dichloromethane (2 ml) under cooling with dry ice-acetone. The mixture was stirred for  
10 20 minutes at the same temperature (-50°C), followed by room temperature for 2 hours. The mixture was poured into ice-water and the dichloromethane layer was separated, dried over magnesium sulfate, and evaporated under reduced pressure. The syrup was purified by column chromatography  
15 on silica gel using a mixed solvent of hexane and ethyl acetate (2:1). The fractions containing the objective compound were collected and evaporated under reduced pressure. The resulting syrup was treated with 4N hydrogen chloride in ethyl acetate (2 ml) and evaporated under  
20 reduced pressure to give (4R,7S,8aS)-4-benzhydryl-7-fluorooctahydropyrrolo[1,2-a]pyrazine dihydrochloride (75 mg).

MASS (APCI): 311 (M+H)<sup>+</sup>, 333 (M+Na) (free)

#### 25 Preparation 64

Triphenylphosphine (860 mg), acetic acid (159 mg) and diisopropyl azodicarboxylate were added successively into a solution of tert-butyl (4R,7R,8aS)-4-benzhydryl-7-hydroxyhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate  
30 (670 mg) in tetrahydrofuran (10 ml) at room temperature. After being stirred for 1 hour at room temperature, the reaction mixture was poured into aqueous saturated sodium hydrogen carbonate. The whole was extracted with ethyl acetate. The extract was washed with brine, dried over  
35 magnesium sulfate and evaporated under reduced pressure.

The resulting residue was purified by silica gel column chromatography with a mixture of hexane and ethyl acetate (2:1 - 3:2) as an eluent to give tert-butyl (4R,7S,8aS)-7-acetoxy-4-benzhydrylhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate.

NMR (CDCl<sub>3</sub>, δ): 1.30-1.43 (11H, m), 2.01-2.04 (3H, m), 2.08-2.79 (6H, m), 3.12 (1H, m), 3.77-4.10 (2H, m), 4.89-5.01 (1H, m), 6.71-7.42 (10H, m)

MASS (APCI): 451 (M+H)<sup>+</sup>

10

#### Preparation 65

Sodium methoxide in methanol (5M, 27 μl) was added into a solution of tert-butyl (4R,7S,8aS)-7-acetoxy-4-benzhydrylhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (628 mg) in methanol (10 ml) at room temperature. After being stirred for 1 hour at the same temperature, the reaction mixture was poured into water (10 ml). The whole was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography with a mixture of hexane and ethyl acetate (1:1) as an eluent to give tert-butyl (4R,7S,8aS)-4-benzhydryl-7-hydroxyhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (521 mg).

NMR (CDCl<sub>3</sub>, δ): 1.20-1.38 (11H, m), 1.80-1.98 (2H, m), 2.14-2.33 (2H, m), 2.43-2.74 (3H, m), 3.10 (1H, br), 3.73 (1H, br), 4.04-4.09 (2H, m), 7.14-7.41 (10H, m)

MASS (APCI): 409 (M+H)<sup>+</sup>

30

#### Preparation 66

Sodium hydride (60% in mineral oil, 14.9 mg) was added into a solution of tert-butyl (4R,7S,8aS)-4-benzhydryl-7-hydroxyhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (126.8 mg) in N,N-dimethylformamide (1.5 ml) under ice-

35



cooling. After being stirred for 0.5 hour at the same temperature, methyl iodide was added to the reaction mixture. And this mixture was stirred for 12 hours at room temperature. Then the reaction mixture was poured into  
5 water (10 ml). The aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The resulting residue was purified by silica gel  
10 column chromatography with a mixture of hexane and ethyl acetate (1:2) as an eluent to give tert-butyl (4R,7S,8aS)-4-benzhydryl-7-methoxyhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (100.5 mg).

NMR (CDCl<sub>3</sub>, δ): 1.38 (11H, br), 1.80-1.88 (1H, m),  
2.04-2.80 (5H, m), 3.14 (3H, s), 3.63-4.18 (4H,  
15 m), 7.14-7.45 (10H, m)

MASS (APCI): 423 (M+H)<sup>+</sup>

#### Preparation 67

The following compound was obtained according to a  
20 similar manner to that of Preparation 63 from tert-butyl (4R,7S,8aS)-4-benzhydryl-7-hydroxyhexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate.

tert-Butyl (4R,7R,8aS)-4-benzhydryl-7-  
25 fluoro-hexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate

NMR (CDCl<sub>3</sub>, δ): 1.22-2.58 (15H, m), 3.12-4.18 (2H, m),  
3.79-4.18 (3H, m), 4.84-5.14 (1H, m), 7.15-7.42  
(10H, m)

MASS (APCI): 411 (M+H)<sup>+</sup>

30

#### Preparation 68

The following compound was obtained according to a similar manner to that of Preparation 3.

35 (4S,7R,8aS)-4-Benzhydryl-7-methoxyoctahydropyrrolo-

[1,2-a]pyrazine dihydrochloride

MASS (APCI): 323 (M+H)<sup>+</sup> (free)

#### Preparation 69

5       The following compound was obtained according to a similar manner to that of Preparation 46 from tert-butyl (2S,3S)-3-hydroxy-2-(N-methoxy-N-methylcarbamoyl)-1-pyrrolidinecarboxylate.

10       tert-Butyl (2S,3S)-2-formyl-3-hydroxy-1-pyrrolidinecarboxylate

NMR (CDCl<sub>3</sub>, δ): 1.47 (9H, s), 1.89-2.04 (1H, m), 3.43-4.48 (6H, m), 9.68 (1H, d)

MASS (ESI): 238 (M+Na)

15

#### Preparation 70

The following compound was obtained according to a similar manner to that of Preparation 25 from tert-butyl (2S,3S)-2-formyl-3-hydroxy-1-pyrrolidinecarboxylate.

20

tert-Butyl (2R,3S)-3-hydroxy-2-[[ (2-methoxybenzyl)amino]methyl]-1-pyrrolidinecarboxylate

NMR (CDCl<sub>3</sub>, δ): 1.47 (9H, m), 1.70-2.20 (5H, m), 2.99-4.52 (5H, m), 3.85 (3H, m), 6.85-6.95 (2H, m),

25

7.20-7.31 (4H, m)

MASS (APCI): 337 (M+1)

#### Preparation 71

30       The following compound was obtained according to a similar manner to that of Preparation 17 from tert-butyl (2R,3S)-3-hydroxy-2-[[ (2-methoxybenzyl)amino]methyl]-1-pyrrolidinecarboxylate.

35       tert-Butyl (2R,3S)-3-hydroxy-2-[N-(2-methoxybenzyl)-N-(2-oxo-3,3-diphenylpropyl)amino]methyl]-1-

pyrrolidinecarboxylate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.41 (9H, m), 1.67-1.80 (3H, m), 2.63-4.18 (9H, m), 5.19 (1H, s), 6.87 (2H, m), 6.84-7.30 (16H, m)

5        MASS (APCI): 545 (M+1)

#### Preparation 72

To a solution of (4R,9aR)-8-acetyl-4-benzhydryl-2-(2-methoxybenzyl)octahydro-2H-pyrazino[1,2-a]pyrazine (5.9 g)  
10 in dichloroethane (60 ml) was added 1-chloroethyl chloroformate (2.3 ml) at room temperature, and the reaction mixture was heated at 70°C for 30 minutes with stirring. After removal of solvent by evaporation, to the resulting residue was added methanol (45 ml), and the  
15 solution was refluxed for 40 minutes. After being concentrated, the residue was triturated with diisopropyl ether. The resulting precipitate was collected by filtration and dried under reduced pressure for 5 hours at 40°C to give (4R,9aR)-8-acetyl-4-benzhydryloctahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride (3.1 g) as  
20 colorless foam.

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.90-2.00 (3H, m), 2.20-4.70 (13H, m), 7.10-7.50 (10H, m), 9.65 (2H, br)

MASS (APCI): 350 (M+H)<sup>+</sup> (free)

25

#### Preparation 73

Under nitrogen atmosphere, to a solution of 5-bromo-2-methoxybenzaldehyde (350 mg) in dimethoxyethane (3.5 ml) were added 3-thiopheneboronic acid (417 mg),  
30 tetrakis(triphenylphosphine)palladium (0) (282 mg), and 2M sodium carbonate (4.9 ml) at room temperature. After being heated at 80°C with stirring for 5 hours, the reaction mixture was poured into mixed solvents of ethyl acetate and water. The organic layer was separated, washed with brine,  
35 dried over magnesium sulfate, and concentrated under

reduced pressure. The resulting residue was purified by column chromatography on silica gel (6 g) using a mixed solvent of hexane and ethyl acetate (10:1). The fractions containing the objective compound were collected and  
5 evaporated under reduced pressure to give 2-methoxy-5-(3-thienyl)benzaldehyde (290 mg) as yellowish oil.

IR (Neat): 3103, 2941, 2854, 1682, 1610, 1495, 1255, 1174  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 3.96 (3H, s), 7.03 (1H, d,  $J=8.7\text{Hz}$ ),  
10 7.30-7.50 (3H, m), 7.79 (1H, dd,  $J=2.5\text{Hz}$ ,  
 $J=8.7\text{Hz}$ ), 8.06 (1H, d,  $J=2.5\text{Hz}$ ), 10.50 (1H, s)

MASS (APCI): 219 (M+H)<sup>+</sup>

#### Preparation 74

15 A solution of 1-fluoro-2-methyl-4-nitrobenzene (10 g) in methanol (200 ml) was hydrogenated over 10% palladium-charcoal (50% wet, 1.0 g) at room temperature under atmospheric pressure for 8 hours. After removal of the catalyst by filtration, the filtrate was evaporated under  
20 reduced pressure to give a syrup. The syrup was dissolved into dichloromethane (200 ml) and thereto triethylamine (16.2 ml) and trifluoroacetic anhydride (14.9 g) were added dropwise. The whole mixture was stirred for 5 hours at room temperature and then washed with water and brine  
25 successively. The organic layer was separated, dried over magnesium sulfate, and evaporated under reduced pressure to give 2,2,2-trifluoro-N-(4-fluoro-3-methylphenyl)acetamide (14.5 g).

NMR ( $\text{CDCl}_3$ ,  $\delta$ ): 2.28 (3H, d,  $J=2.0\text{Hz}$ ), 6.96-7.05 (1H,  
30 m), 7.31-7.46 (1H, m), 8.09 (1H, br s)

MASS (APCI): 244 (M+Na)<sup>+</sup>

#### Preparation 75

A mixture of 2,2,2-trifluoro-N-(4-fluoro-3-  
35 methylphenyl)acetamide (14.3 g) and triphenylphosphine

(19.5 g) in tetrachloromethane (140 ml) was stirred for 17 hours at 100°C. An additional triphenylphosphine (5 g) was added to the mixture and the whole was stirred for 5 hours and finally triphenylphosphine (5 g) was added to the mixture, and the whole was stirred further for 15 hours at 100°C. After being cooled to room temperature hexane was added to the reaction mixture and the whole was stirred for 0.5 hour under ice-cooling. The resulting precipitate was removed by filtration and washed with hexane. The combined filtrate and washing were evaporated under reduced pressure below 20°C. A mixture of the syrup obtained and sodium azide (10.6 g) in acetic acid (100 ml) was stirred at room temperature for 7 hours, followed by at 70°C for 17 hours. After being cooled to room temperature, the mixture was poured into ice-water, and extracted with dichloromethane. The organic layer was separated, dried over magnesium sulfate, and evaporated under reduced pressure. The syrup was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (100:1 - 5:1). The fractions containing the objective compound were collected to give 1-(4-fluoro-3-methylphenyl)-5-(trifluoromethyl)-1H-tetrazole (15.2 g) as a syrup.

NMR (CDCl<sub>3</sub>,  $\delta$ ): 2.40 (3H, d, J=2.0Hz), 7.19-7.63 (3H, m)

MASS: 247 (M+H)<sup>+</sup> 219

#### Preparation 76

2,2'-Azobis(4-methoxy-2,4-dimethylvaleronitrile) (50 mg) was added by three portions to the mixture of 1-(4-fluoro-3-methylphenyl)-5-(trifluoromethyl)-1H-tetrazole and N-bromophthalimide (1.44 g) in dichloromethane (16 ml) at 30°C and the whole was stirred at reflux for 3 hours. After being cooled to room temperature, the mixture was washed with aqueous sodium hydrogen carbonate and aqueous sodium thiosulfate successively. The organic layer was separated,

dried over magnesium sulfate, and evaporated under reduced pressure to give a crude 1-[3-(bromomethyl)-4-fluorophenyl]-5-(trifluoromethyl)-1H-tetrazole (3:7).

5 NMR (CDCl<sub>3</sub>, δ): 4.54 (2H, d, J=1.0Hz), 7.19-7.63 (3H, m)

Preparation 77

To a solution of (2S)-2-ethoxycarbonylpiperazine-1-carboxylic acid 1-tert-butyl ester D-tartarate (9.56 g) in tetrahydrofuran (90 ml) and water (90 ml) was added sodium bicarbonate (7.87 g) under ice-cooling. Benzyl chloroformate (4.01 ml) was added dropwise to the solution over 2 minutes at the same temperature, and stirred at room temperature for 15 minutes. Ethyl acetate (60 ml) and sodium chloride (5 g) was added to the mixture. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure to give (2S)-2-ethoxycarbonylpiperazine-1,4-dicarboxylic acid 4-benzyl ester 1-tert-butyl ester (10.4 g) as a colorless oil.

20 NMR (CDCl<sub>3</sub>, δ): 1.10-1.60 (12H, m), 2.60-4.80 (9H, m),  
5.00-5.30 (2H, m), 7.20-7.40 (5H, m)  
MASS (API-ES): 415 (M+Na)<sup>+</sup>

### Preparation 78

25 Under nitrogen atmosphere, to a solution of (2S)-2-ethoxycarbonylpiperazine-1,4-dicarboxylic acid 4-benzyl ester 1-tert-butyl ester (9.35 g) was added portionwise lithium borohydride (1.82 g), and the reaction mixture was stirred for 90 minutes. After methanol (2.32 ml) was added  
30 dropwise to the solution under ice-cooling, the mixture was stirred at room temperature for 17 hours. 1N Hydrochloric acid (80 ml) was added dropwise under ice-cooling, and ethyl acetate (100 ml) and sodium chloride (6 g) was added to it. The organic layer was washed with brine, dried over  
35 magnesium sulfate, and evaporated under reduced pressure to

give colorless oil. The oil was purified by column chromatography on silica gel (90 g) using a mixed solvent of hexane and ethyl acetate (3:2). The fractions containing the objective compound were collected and  
5 evaporated under reduced pressure to give (2S)-2-(hydroxymethyl)piperazine-1,4-dicarboxylic acid 4-benzyl ester 1-tert-butyl ester (8.40 g) as a colorless oil.

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.46 (9H, s), 2.40-4.30 (10H, m), 5.10-5.30 (2H, m), 7.30-7.50 (5H, m)

10 MASS (API-ES): 373 (M+Na)<sup>+</sup>

#### Preparation 79

Under nitrogen atmosphere, to a solution of oxalyl chloride (1.64 ml) in dichloromethane (34 ml) under -65°C,  
15 was added dropwise a solution of dimethyl sulfoxide (2.0 ml) in dichloromethane (15 ml) and stirred for 10 minutes at the same temperature. A solution of (2S)-2-(hydroxymethyl)piperazine-1,4-dicarboxylic acid 4-benzyl ester 1-tert-butyl ester (3.29 g) in dichloromethane (24  
20 ml) was dropped into the above solution over 5 minutes under -65°C. The reaction mixture was stirred at the same temperature for 15 minutes, then stirred at -45°C for 90 minutes. Triethylamine (7.85 ml) was added to the solution under -40°C, and the mixture was stirred at 0°C for 20  
25 minutes. The mixture was poured into saturated aqueous ammonium chloride (100 ml). The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give (2R)-2-formylpiperazine-1,4-dicarboxylic acid 4-benzyl ester 1-tert-butyl ester (3.33 g) as a colorless syrup.

30 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.40-1.70 (9H, m), 2.85-3.30 (3H, m), 3.70-4.80 (4H, m), 5.05-5.30 (2H, m), 7.30-7.40 (5H, m), 9.58 (1H, s)

MASS (API-ES): 371 (M+Na)<sup>+</sup>

#### 35 Preparation 80

A solution of 3-bromo-1,1-diphenyl-2-propanone (0.5 g) in tetrahydrofuran (10 ml) was added to a mixture of (2-methoxy-benzyl)amine (1.13 ml) and N,N-diisopropylethylamine (0.602 ml) in tetrahydrofuran (12 ml) over 0.5 hour at room temperature. After being stirred at room temperature for 1.5 hours, the mixture was concentrated under reduced pressure to half volume and the resulting mixture was poured into ice-water (10 ml) and extracted with ethyl acetate (10 ml X 2). The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 3-[(2-methoxybenzyl)amino]-1,1-diphenylpropan-2-one (483 mg) as a colourless syrup.

NMR (CDCl<sub>3</sub>, δ): 3.63 (2H, s), 3.73 (2H, s), 3.79 (3H, s), 5.13 (1H, s), 6.82-7.36 (14H, m)

MASS (APCI): 346 (M+H)<sup>+</sup>

#### Preparation 81

Under nitrogen atmosphere, to a solution of (2R)-2-formylpiperazine-1,4-dicarboxylic acid 4-benzyl ester 1-tert-butyl ester (2.64 g) and 3-(2-methoxybenzylamino)-1,1-diphenylpropan-2-one (3.66 g) in dichloromethane (30 ml) was added acetic acid (0.607 ml) and sodium tritacetoxymethylborohydride (4.82 g) under ice-cooling, and then it was stirred at room temperature for 3 hours. The reaction mixture was poured into aqueous sodium hydrogen carbonate (100 ml) and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (82 g) using a mixed solvent of hexane and ethyl acetate (3:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2S)-2-[[N-(2-methoxybenzyl)-N-(2-oxo-3,3-diphenylpropyl)amino]methyl]piperazine-1,4-dicarboxylic



acid 4-benzyl ester 1-tert-butyl ester (3.24 g) as a syrup.

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.40-1.65 (9H, m), 2.65-5.40 (19H, m),

6.70-7.40 (19H, m)

MASS (APCI): 678 (M+H)<sup>+</sup>

5

#### Preparation 82

The following compound was obtained according to a similar manner for Preparation 72.

10 (4R, 9aS)-4-Benzhydryl-8-(benzyloxycarbonyl)octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.20-5.00 (13H, m), 5.07 (2H, s),

7.15-7.45 (15H, m), 9.53 (2H, br)

MASS (APCI): 442 (M+H)<sup>+</sup> (free)

15

#### Preparation 83

The following compound was obtained according to a similar manner to that of Preparation 34.

20 Benzyl [1-(N-methoxy-N-methylcarbamoyl)cyclopentyl]-carbamate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.61-1.74 (4H, m), 1.86-2.00 (2H, m),

2.22-2.40 (2H, m), 3.13 (3H, s), 3.53 (3H, s),

5.07 (1H, br s), 5.10 (2H, s), 7.29-7.35 (5H, m)

25 MASS (APCI): 635 (2M+Na), 329 (M+Na)<sup>+</sup>

#### Preparation 84

The following compounds were obtained according to a similar manner to that of Preparation 35.

30

(1) Benzyl (1-formylcyclopentyl)carbamate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.61-2.17 (8H, m), 5.10 (2H, s), 5.26

(1H, br s), 7.29-7.35 (5H, m), 9.53 (1H, s)

MASS (APCI): 204, 248 (M+H)<sup>+</sup>

35

(2) Benzyl [1-[(benzylamino)methyl]cyclopentyl]carbamate  
NMR (CDCl<sub>3</sub>, δ): 1.50-2.04 (9H, m), 2.76 (2H, s), 3.79  
(2H, s), 5.05 (2H, s), 5.18 (1H, br s), 7.20-7.35  
(10H, m)

5 MASS (APCI): 339 (M+H)<sup>+</sup>, 231

(3) Benzyl [1-[[N-benzyl-N-(2-oxo-3,3-  
diphenylpropyl)amino]methyl]cyclopentyl]carbamate  
NMR (CDCl<sub>3</sub>, δ): 1.50-2.04 (8H, m), 2.92 (2H, s), 3.48  
10 (2H, s), 3.75 (2H, s), 4.90-5.00 (4H, s), 7.20-  
7.35 (20H, m)

MASS (APCI): 547 (M+H)<sup>+</sup>, 406

#### Preparation 85

15 The following compound was obtained according to a  
similar manner to that of Preparation 18.

7-Benzhydryl-6,9-diazaspiro[4.5]decane

MASS (APCI): 307 (M+H)<sup>+</sup> (free)

20

#### Preparation 86

The following compound was obtained according to a  
similar manner to that of Preparation 35.

25 Benzyl [2-(benzylamino)-1,1-dimethylethyl]carbamate  
NMR (CDCl<sub>3</sub>, δ): 1.28 (6H, s), 2.63 (1H, s), 3.81 (2H,  
s), 3.79 (2H, s), 5.04 (2H, s), 5.42 (1H, br s),  
7.20-7.35 (10H, m)

MASS (APCI): 313 (M+H)<sup>+</sup>

30

#### Preparation 87

The following compound was obtained according to a  
similar manner to that of Preparation 17.

35 Benzyl [2-[N-benzyl-N-(2-oxo-3,3-phenylpropyl)amino]-

## 1,1-dimethylethyl]carbamate

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.28 (6H, s), 2.77 (2H, s), 3.53 (2H, s), 3.78 (2H, s), 5.00 (2H, s), 5.44 (1H, br s), 7.20-7.35 (20H, m)

5 MASS (APCI): 521 (M+H)<sup>+</sup>, 413

Preparation 88

The following compound was obtained according to a similar manner to that of Preparation 18.

10

## 6-Benzhydryl-2,2-dimethylpiperazine

IR (KBr): 3400, 1648, 1504 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 0.96 (3H, s), 1.29 (3H, s), 2.28-2.39 (1H, m), 2.53 (1H, d, J=12.2Hz), 2.60 (1H, d, J=12.2Hz), 2.72 (1H, d, J=11.0Hz), 3.62-3.74 (2H, m), 7.14-7.38 (10H, m)

15

MASS (APCI): 281 (M+H)<sup>+</sup> (free)

Preparation 89

20

The following compound was obtained according to a similar manner to that of Example 4.

2-[2-Benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1-piperazinyl]acetic acid

25

MASS (APCI): 567 (M+H)<sup>+</sup>

Dihydrochloride of the above compound

IR (KBr, FT-IR): 1615, 1440, 1320, 1265, 1235 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.70-5.15 (12H, m), 3.84 (3H, s), 7.10-8.10 (13H, m), 10.36 (1H, br s)

30

MASS (APCI): 567 (M+H)<sup>+</sup> (free)

Preparation 90

Sodium triacetoxyborohydride (163 mg) was added to a mixture of bis(acetic acid) salt of (7R,8aS)-4-benzhydryl-

35

7-[(tert-butyldimethylsilyl)oxy]octahydropyrrolo[1,2-a]pyrazine (0.38 g) and 2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzaldehyde (210 mg) in dichloromethane, and the whole was stirred for 3 hours at room temperature.

5 The mixture was washed with aqueous sodium hydrogen carbonate, dried over magnesium sulfate and concentrated under reduced pressure. The syrup was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (4:1). The later eluting  
10 fractions were collected and evaporated under reduced pressure to give colorless oil of (4R,7R,8aS)-4-benzhydryl-7-[(tert-butyldimethylsilyl)oxy]-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-octahydropyrrolo[1,2-a]pyrazine (0.18 g).

15 NMR (CDCl<sub>3</sub>,  $\delta$ ): -0.20 (3H, s), -0.11 (3H, m), 0.75 (9H, m), 1.58-1.74 (4H, m), 2.18 (1H, dd, J=4.7 and 9.6Hz), 2.26 (1H, dd, J=3.3 and 11.3Hz), 2.31 (1H, d, J =11.3Hz), 2.69 (1H, dd, J=3.0 and 10.6Hz), 2.96 (1H, dd, J=6.7 and 9.5Hz), 3.25 (1H, d, J=14.8Hz),  
20 3.30-3.50 (1H, m), 3.69 (1H, d, J=10.6Hz), 3.87 (3H, s), 4.20-4.25 (1H, m), 4.66 (1H, d, J=10.8Hz), 6.94-7.40 (12H, m), 7.54 (1H, d, J=2.6Hz)

MASS (APCI-ES): 679 (M+H)<sup>+</sup>

25

The earlier eluting fractions were collected and evaporated under reduced pressure to give colorless oil of (4S,7R,8aS)-4-benzhydryl-7-[(tert-butyldimethylsilyl)oxy]-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazine (0.15 g).

30 NMR (CDCl<sub>3</sub>,  $\delta$ ): -0.20 (3H, s), -0.11 (3H, m), 0.75 (9H, m), 1.56-1.95 (6H, m), 2.47 (1H, d, J=11.2Hz), 2.64-2.92 (2H, m), 3.36-3.60 (3H, m), 2.78 (3H, s), 3.92 (1H, d, J=11.1Hz), 4.07-4.17 (1H, m),  
35 6.92 (1H, d, J=8.8Hz), 7.05-7.45 (12H, m)

MASS (APCI-ES): 679 (M+H)<sup>+</sup> (free)

#### Preparation 91

The following compound was obtained according to a similar manner to that of Preparation 56 from (4R,8S,8aR)-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazin-8-ol.

(4R,8R,8aR)-8-Azido-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazine

MASS (APCI): 590 (M+1)

#### Preparation 92

The following compound was obtained according to a similar manner to that of Preparation 64 from (4R,8S,8aR)-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazin-8-ol.

(4R,8R,8aR)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazin-8-yl acetate

NMR (CDCl<sub>3</sub>, δ): 1.91-2.23 (5H, m), 2.03 (3H, s), 2.43 (2H, br), 2.63-2.89 (2H, m), 3.24 (1H, br), 3.42-3.64 (2H, d x 2, J=15Hz), 3.78 (3H, s), 4.09 (1H, m), 5.18 (1H, m), 6.90-7.42 (13H, m)

MASS (APCI) : 607 (M+1)

#### Preparation 93

The following compound was obtained according to a similar manner to that of Preparation 56 from (4R,8R,8aR)-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazin-8-ol.

(4R,8S,8aR)-8-Azido-4-benzhydryl-2-[2-methoxy-5-[5-

(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo-[1,2-a]pyrazine

MASS (APCI): 590 (M+1) (free)

5 Preparation 94

To a mixture of (4R,9aS)-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine trihydrochloride (80 mg), cyclopentanecarboxylic acid (16.9  $\mu$ l), 1-  
10 hydroxybenzotriazole hydrate (23 mg), and triethylamine (79  $\mu$ l) in dichloromethane (1 ml) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride at room temperature. After stirring at room temperature overnight, the mixture was quenched with aqueous saturated  
15 sodium hydrogen carbonate and extracted with dichloromethane. The extract was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified with preparative TLC (methanol/chloroform = 1/9) to give an oil. To a solution of the oil in ethyl  
20 acetate (1 ml) was added 4N hydrogen chloride in ethyl acetate (0.2 ml) and hexane (20 ml). After stirring for 30 minutes, the precipitate was collected by filtration and dried under reduced pressure at 50°C for 5 hours to give  
25 (4R,9aR)-4-benzhydryl-8-cyclopentanecarbonyl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride (63.9 mg) as a powder.

mp: 170-178°C, decomp.

$[\alpha]_D^{27}$ : -37.83 (C, 0.115, MeOH)

30 IR (KBr) 1647  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.40-1.80 (8H, m), 2.20-4.50 (16H, m),  
3.80 and 3.82 (total 3H, s), 7.15-7.82 (13H, m)

MASS (APCI+): 660.2 (MH+) (free)

35 Example 1

A mixture of 3-benzhydryl-1-(2-methoxybenzyl)-piperazine dihydrochloride (44.5 mg), bromoacetamide (20.7 mg) and potassium carbonate (41.5 mg) in N,N-dimethylformamide (5 ml) was stirred at room temperature for 18 hours. The mixture was partitioned between ethyl acetate and 2N sodium hydroxide. The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (70:1). The fractions containing the objective compound were collected, evaporated under reduced pressure and treated with 4N hydrogen chloride in ethyl acetate solution to give 2-benzhydryl-1-carbamoylmethyl-4-(2-methoxybenzyl)piperazine dihydrochloride (21.6 mg) as a colorless powder.

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.79-4.20 (14H, m), 5.08 (1H, d,  $J=12.3\text{Hz}$ ), 5.85-5.96 (2H, m), 6.83-7.63 (14H, m), 10.05-10.32 (2H, m)

MASS (APCI): 430 (M+H)<sup>+</sup> (free)

#### Example 2

Sodium triacetoxyborohydride (127 mg) was added portionwise to a mixture of 2-benzhydrylpiperazine dihydrochloride (97.6 mg), N,N-diisopropylethylamine (0.104 ml) and 2-methoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]benzaldehyde (61.2 mg) in a mixture of dichloromethane (5 ml) and acetic acid (1 drop) at 0°C and the whole was stirred at 5°C ~ room temperature overnight. The mixture was partitioned between ethyl acetate and 2N sodium hydroxide. The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (70:1). The fractions containing the objective compound were collected,

evaporated under reduced pressure and treated with 4N  
hydrogen chloride in ethyl acetate solution to give 3-  
benzhydryl-1-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-  
1-yl]benzyl]piperazine dihydrochloride (74 mg) as a  
5 colorless powder.

NMR (DMSO-d<sub>6</sub>, δ): 2.60-4.81 (14H, m), 7.17-7.50 (11H,  
m), 7.22-7.75 (2H, m)

MASS (APCI): 509 (M+H)<sup>+</sup> (free)

10 Example 3

The following compounds were obtained according to a  
similar manner to that of Example 2.

(1) 3-Benzhydryl-1-(2-methoxybenzyl)piperazine  
15 dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.60-4.71 (14H, m), 6.92-7.03 (2H, m),  
7.29-7.46 (12H, m)

MASS (APCI): 373 (M+H)<sup>+</sup> (free)

20 (2) 3-Benzhydryl-1-[2-methoxy-5-(trifluoromethoxy)benzyl]-  
piperazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.80-4.73 (14H, m), 7.07-7.51 (13H,  
m)

MASS (APCI): 457 (M+H)<sup>+</sup> (free)

25

(3) 3-Benzhydryl-1-[2-methoxy-5-(trifluoromethyl)benzyl]-  
piperazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 3.02-4.72 (14H, m), 7.17-7.82 (13H,  
m)

30 MASS (APCI): 441 (M+H)<sup>+</sup> (free)

(4) 3-Benzhydryl-1-(5-bromo-2-methoxybenzyl)piperazine  
dihydrochloride

35 NMR (DMSO-d<sub>6</sub>, δ): 3.00-4.70 (14H, m), 7.26-7.64 (13H,  
m)



MASS (APCI): 451 (M+H)<sup>+</sup> (free)

(5) 3-Benzhydryl-1-[2-methoxy-5-(1H-tetrazol-1-yl)benzyl]piperazine dihydrochloride

5 NMR (DMSO-d<sub>6</sub>, δ): 2.95-4.65 (15H, m), 7.18-7.95 (13H, m)

MASS (APCI): 441 (M+H)<sup>+</sup> (free)

(6) 2-Benzhydryl-4-[2-methoxy-5-(trifluoromethoxy)benzyl]-morpholine hydrochloride

10 NMR (DMSO-d<sub>6</sub>, δ): 2.90-4.62 (13H, m), 7.04-7.57 (3H, m)

MASS (APCI): 458 (M+H)<sup>+</sup> (free)

(7) 2-Benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]morpholine hydrochloride

15 NMR (DMSO-d<sub>6</sub>, δ): 2.80-4.55 (13H, m), 7.18-7.34 (11H, m), 8.13 (2H, m)

MASS (APCI): 510 (M+H)<sup>+</sup> (free)

(8) 6-Benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]piperazin-2-one hydrochloride

20 NMR (DMSO-d<sub>6</sub>, δ): 2.84-4.55 (12H, m), 7.24-7.38 (11H, m), 7.75-7.79 (2H, m)

MASS (APCI): 523 (M+H)<sup>+</sup> (free)

25

(9) 5-Benzhydryl-7-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine dihydrochloride

30 NMR (DMSO-d<sub>6</sub>, δ): 2.86 (2H, m), 3.57-3.76 (3H, m), 3.83 (3H, s), 4.28 (1H, d, J=16.5Hz), 4.48 (1H, d, J=11.0Hz), 5.49 (1H, d, J=10.6Hz), 6.26 (1H, s), 7.21-7.38 (12H, m), 7.67-7.77 (2H, m)

MASS (APCI): 546 (M+H)<sup>+</sup> (free)

35 (10) 6-Benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-

tetrazol-1-yl]benzyl]-3-methylpiperazin-2-one  
hydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.42 (3H, m), 2.72-4.55 (11H, m),  
7.11-7.34 (10H, m), 7.59-7.68 (3H, m)

5 MASS (APCI): 537 (M+H)<sup>+</sup> (free)

(11) 6-Benzhydryl-3,3-dimethyl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]piperazin-2-one hydrochloride

10 NMR (DMSO-d<sub>6</sub>, δ): 1.24 (3H, s), 1.35 (3H, s), 3.54-4.40  
(4H, m), 3.89 (3H, s), 4.55 (2H, s), 6.37 (1H, br  
s), 7.05-7.32 (9H, m), 7.59-7.78 (4H, m)

MASS (APCI): 551 (M+H)<sup>+</sup> (free)

15 (12) (3S)-3-Benzhydryl-1-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]piperazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.60-4.81 (14H, m), 7.17-7.50 (11H,  
m), 7.22-7.75 (2H, m)

MASS (APCI): 509 (M+H)<sup>+</sup> (free)

20

(13) (2S)-2-Benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1-methylpiperazine dihydrochloride

25 NMR (DMSO-d<sub>6</sub>, δ): 2.28-4.73 (16H, m), 7.15-7.40 (9H, m),  
7.55 (2H, m), 7.71 (2H, m)

MASS (APCI): 523 (M+H)<sup>+</sup> (free)

(14) (8aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazine dihydrochloride

30 NMR (DMSO-d<sub>6</sub>, δ): 1.23-3.49 (11H, m), 3.64-3.96 (5H, m),  
3.74 (3H, s), 4.23 (1H, d, J=9.5Hz), 7.16-7.67  
(13H, m)

35 MASS (APCI): 549 (M+H)<sup>+</sup> (free)

- (15) (2R)-2-Benzhydryl-4-(2-methoxybenzyl)-1-methylpiperazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 2.66-4.78 (16H, m), 6.89-6.99 (2H, m),  
5 7.26-7.55 (12H, m)  
MASS (APCI): 387 (M+H)<sup>+</sup> (free)
- (16) (2R)-2-Benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1-methylpiperazine  
10 dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 2.28-4.73 (16H, m), 7.15-7.40 (9H, m),  
7.55 (2H, m), 7.71 (2H, m)  
MASS (APCI): 523 (M+H)<sup>+</sup> (free)
- 15 (17) (3R)-3-Benzhydryl-1-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]piperazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 2.60-4.81 (14H, m), 7.17-7.50 (11H, m),  
7.22-7.75 (2H, m)  
MASS (APCI): 509 (M+H)<sup>+</sup> (free)  
20
- (18) (2S)-2-Benzhydryl-4-[2-(trifluoromethyl)benzyl]-1-methylpiperazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 2.20-5.10 (13H, m), 7.08-8.14 (14H, m)  
25 MASS (APCI): 425 (M+H)<sup>+</sup> (free)
- (19) (2R)-2-Benzhydryl-4-[2-(trifluoromethyl)benzyl]-1-methylpiperazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 2.20-5.10 (13H, m), 7.08-8.14 (14H, m)  
30 m)  
MASS (APCI): 425 (M+H)<sup>+</sup> (free)
- (20) (4R, 8aS)-4-Benzhydryl-2-(2,6-dimethoxybenzyl)-octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
35 NMR (DMSO-d<sub>6</sub>, δ): 1.58-4.51 (23H, m), 6.63 (1H, d,

$J=8.4\text{Hz}$ ), 7.26-7.51 (12H, m)

MASS (APCI): 443 (M+H)<sup>+</sup> (free)

- 5 (21) (4R,8aS)-4-Benzhydryl-2-[2-methoxy-5-(trifluoromethoxy)benzyl]octahydropyrrolo[1,2-a]-pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.60-2.20 (3H, m), 2.79-4.20 (17H, m),  
7.02-7.53 (13H, m)  
MASS (APCI): 497 (M+H)<sup>+</sup> (free)
- 10 (22) (4R,8aS)-4-Benzhydryl-2-(2-ethoxybenzyl)-octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.20-4.30 (22H, m), 6.92-7.50 (14H, m)  
MASS (APCI): 427 (M+H)<sup>+</sup> (free)
- 15 (23) (4R,8aS)-4-Benzhydryl-2-(2,4-dimethoxybenzyl)-octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.50-4.11 (17H, m), 3.78 (6H, s),  
20 6.50 (3H, m), 7.31-7.49 (10H, m)  
MASS (APCI): 443 (M+H)<sup>+</sup> (free)
- 25 (24) (4R,8aS)-4-Benzhydryl-2-[(2,2-difluorobenzo[1,3]-dioxol-4-yl)methyl]octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.50-2.20 (4H, m), 2.75-4.56 (17H, m),  
7.17-7.82 (13H, m)  
MASS (APCI): 463 (M+H)<sup>+</sup> (free)
- 30 (25) (4R,8aS)-4-Benzhydryl-2-(2,4,6-trimethoxybenzyl)-octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.50-2.20 (2H, m), 2.80-4.00 (15H, m),  
3.80 (9H, s), 6.19 (2H, s), 7.31-7.46 (10H, m)  
MASS (APCI): 473 (M+H)<sup>+</sup> (free)
- 35

- (26) (4R, 8aS)-4-Benzhydryl-2-(2,4,5-trimethoxybenzyl)-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.40-2.20 (3H, m), 2.55-4.20 (14H, m),  
3.80 (9H, s), 6.61 (1H, s), 7.25-7.49 (11H, m)  
5 MASS (APCI): 473 (M+H)<sup>+</sup> (free)
- (27) (4R, 8aS)-4-Benzhydryl-2-[2-methoxy-5-(  
(trifluoromethyl)benzyl)]octahydropyrrolo[1,2-  
a]pyrazine dihydrochloride  
10 NMR (DMSO-d<sub>6</sub>, δ): 1.50-2.20 (3H, m), 2.88-5.09 (14H, m),  
3.73 (3H, s), 7.13-7.79 (13H, m)  
MASS (APCI): 481 (M+H)<sup>+</sup> (free)
- (28) (4R, 8aS)-4-Benzhydryl-2-(5-bromo-2,4-dimethoxybenzyl)-  
15 octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.60-1.98 (3H, m), 2.94-4.40 (14H, m),  
3.89 (6H, s), 6.67 (1H, s), 7.26-7.64 (11H, m)  
MASS (APCI): 521 (M+H)<sup>+</sup> (free)
- (29) (4R, 8aS)-4-Benzhydryl-2-(5-bromo-2,4-methoxybenzyl)-  
20 octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.64-2.06 (3H, m), 2.50-4.85 (14H, m),  
3.62 (3H, s), 6.90-7.60 (13H, m)  
MASS (APCI): 493 (M+H)<sup>+</sup> (free)
- (30) (4R, 8aS)-4-Benzhydryl-2-(5-isopropyl-2-methoxybenzyl)-  
25 octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.17 (6H, d, J=5.4Hz), 1.50-2.20 (3H,  
m), 2.80-4.15 (18H, m), 6.86-7.50 (13H, m)  
30 MASS (APCI): 455 (M+H)<sup>+</sup> (free)
- (31) (4R, 8aS)-4-Benzhydryl-2-(2,4-dimethoxy-5-  
methylbenzyl)octahydropyrrolo[1,2-a]pyrazine  
dihydrochloride  
35 NMR (DMSO-d<sub>6</sub>, δ): 1.55-2.10 (3H, m), 2.03 (3H, s),

3.00-4.55 (14H, m), 3.83 (6H, s), 6.53 (1H, s),  
7.14-7.49 (11H, m)

MASS (APCI): 457 (M+H)<sup>+</sup> (free)

5 (32) 2-(((4R,8aS)-4-Benzhydrylhexahydropyrrolo[1,2-a]-  
pyrazine-2-yl)methyl]benzonitrile dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.80-2.20 (3H, m), 2.40-4.58 (14H, m),  
7.15-7.79 (14H, m)  
MASS (APCI): 408 (M+H)<sup>+</sup> (free)

10

(33) 2-(((4R,8aS)-4-Benzhydrylhexahydropyrrolo[1,2-a]-  
pyrazine-2-yl)methyl)benzoic acid methyl ester  
dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.50-2.20 (3H, m), 2.80-4.60 (14H, m),  
15 3.82 (3H, s), 7.17-7.84 (14H, m)  
MASS (APCI): 441 (M+H)<sup>+</sup> (free)

(34) (4R,8aS)-4-Benzhydryl-2-(2-iodobenzyl)-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
20 NMR (DMSO-d<sub>6</sub>, δ): 1.55-2.20 (3H, m), 2.60-4.51 (14H, m),  
7.01-7.82 (14H, m)  
MASS (APCI): 509 (M+H)<sup>+</sup> (free)

(35) (4R,8aS)-4-Benzhydryl-2-(2-nitrobenzyl)-  
25 octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.55-2.20 (3H, m), 2.60-4.40 (14H, m),  
7.23-7.88 (14H, m)  
MASS (APCI): 428 (M+H)<sup>+</sup> (free)

30 (36) (4R,8aS)-4-Benzhydryl-2-[2-(trifluoromethyl)benzyl]-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.60-2.20 (3H, m), 2.70-4.67 (14H, m),  
7.12-7.77 (14H, m)  
MASS (APCI): 451 (M+H)<sup>+</sup> (free)

35

- (37) (4R, 8aS)-4-Benzhydryl-2-(2,5-dimethoxybenzyl)-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.50-2.20 (3H, m), 2.80-5.00 (14H, m),  
3.72 (6H, s), 6.75-7.54 (13H, m)  
5 MASS (APCI): 443 (M+H)<sup>+</sup> (free)
- (38) (4R, 8aS)-4-Benzhydryl-2-(2,6-diethoxybenzyl)-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.21 (6H, t, J=6.7Hz), 1.50-2.20 (3H,  
10 m), 2.76-4.46 (18H, m), 6.58 (1H, d, J=8.4Hz),  
7.30-7.46 (12H, m)  
MASS (APCI): 471 (M+H)<sup>+</sup> (free)
- (39) (4R, 8aS)-4-Benzhydryl-2-[2-ethoxy-5-[5-  
15 (trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.14-1.40 (3H, m), 1.50-2.10 (3H, m),  
2.73 (2H, br), 3.40-4.30 (14H, m), 7.17-7.69 (13H,  
m)  
20 MASS (APCI): 563 (M+H)<sup>+</sup> (free)
- (40) (4R, 8aS)-4-Benzhydryl-2-[2-propoxy-5-[5-  
(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
25 NMR (DMSO-d<sub>6</sub>, δ): 0.96 (3H, t, J=7.4Hz), 1.60-2.07 (5H,  
m), 2.78 (2H, br s), 3.40-4.56 (14H, m), 7.17-  
7.70 (13H, m)  
MASS (APCI): 577 (M+H)<sup>+</sup> (free)
- (41) (4R, 8aS)-4-Benzhydryl-2-[2-isopropoxy-5-[5-  
30 (trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.16-1.33 (6H, m), 3.20-3.80 (18H, m),  
7.20-7.60 (13H, m)  
35 MASS (APCI): 577 (M+H)<sup>+</sup> (free)

- (42) (4R, 8aS)-4-Benzhydryl-2-[2-(2-methoxyethoxy)-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
5 NMR (DMSO-d<sub>6</sub>, δ): 1.40-2.10 (3H, m), 2.70 (1H, br),  
3.31-4.56 (20H, m), 7.15-7.68 (13H, m)  
MASS (APCI): 593 (M+H)<sup>+</sup> (free)
- (43) (4R, 8aS)-4-Benzhydryl-2-[2-cyclopentyloxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-  
10 octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.61-2.06 (11H, m), 2.70 (1H, br),  
3.30-4.84 (14H, m), 7.20-7.66 (13H, m)  
MASS (APCI): 603 (M+H)<sup>+</sup> (free)
- (44) (4R, 8aS)-4-Benzhydryl-2-[2-fluoromethoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.50-2.20 (3H, m), 2.60 (1H, br),  
20 3.20-4.48 (13H, m), 5.74 (1H, br), 6.00 (1H, br),  
7.14-7.74 (13H, m)  
MASS (APCI): 567 (M+H)<sup>+</sup> (free)
- (45) (4R, 8aS)-4-Benzhydryl-2-(2,4,5-trimethylbenzyl)-  
25 octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 425 (M+H)<sup>+</sup>
- (46) (4R, 8aS)-4-Benzhydryl-2-[3,5-bis(trifluoromethyl)-  
benzyl]octahydropyrrolo[1,2-a]pyrazine  
30 MASS (APCI): 519 (M+H)<sup>+</sup>
- (47) (4R, 8aS)-4-Benzhydryl-2-[2,5-bis(trifluoromethyl)-  
benzyl]octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 519 (M+H)<sup>+</sup>



- (48) (4R, 8aS)-4-Benzhydryl-2-[2-chloro-5-(trifluoromethyl)-benzyl]octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 485 (M+H)<sup>+</sup>
- 5 (49) (4R, 8aS)-4-Benzhydryl-2-(3,5-dimethylbenzyl)-octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 411 (M+H)<sup>+</sup>
- 10 (50) (4R, 8aS)-4-Benzhydryl-2-[2-fluoro-5-(trifluoromethyl)-benzyl]octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 469 (M+H)<sup>+</sup>
- 15 (51) (4R, 8aS)-4-Benzhydryl-2-[2-methoxy-5-(methanesulfonyl)benzyl]octahydropyrrolo[1,2-a]-pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 3.19 (3H, s), 3.72 (3H, s), 1.20-5.10 (17H, m), 7.16-7.40 (9H, m), 7.50-7.55 (2H, m), 7.99 (1H, dd, J=2.5, 8.6Hz), 8.05 (1H, br s)  
MASS (APCI): 491 (M+H)<sup>+</sup> (free)
- 20 (52) (4R, 8aS)-4-Benzhydryl-2-[2-hydroxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.20-4.80 (16H, m), 7.04-7.57 (13H, m)  
MASS (APCI): 535 (M+H)<sup>+</sup> (free)
- 25 (53) (4R, 8aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.50-5.00 (15H, m), 3.76 (3H, s), 7.21-7.57 (13H, m)  
MASS (APCI): 549 (M+H)<sup>+</sup> (free)
- 30 (54) [2-((4R, 8aS)-4-Benzhydrylhexahydropyrrolo[1,2-a]-

pyrazin-2-ylmethyl)-4-[5-(trifluoromethyl)-1H-tetrazol-1-yl]phenoxy]acetic acid methyl ester

NMR (CDCl<sub>3</sub>, δ): 1.10-2.10 (7H, m), 2.30-2.46 (2H, m),  
2.60-2.70 (1H, m), 2.93 (1H, d, J=10.0Hz), 3.27-  
3.43 (1H, m), 3.53 (1H, d, J=15.4Hz), 3.59 (1H, d,  
J=15.4Hz), 3.81 (3H, s), 4.00 (1H, d, J=9.1Hz),  
4.60 (2H, s), 6.79 (1H, d, J=8.8Hz), 7.00-7.45  
(11H, m), 7.51 (1H, d, J=2.6Hz)

MASS (APCI): 607 (M+H)<sup>+</sup>

(55) (3RS,4aSR,8aSR)-3-Benzhydryl-1-[2-methoxy-5-(5-(trifluoromethyl)-1H-tetrazol-1-yl)benzyl]-decahydroquinoxaline

NMR (CDCl<sub>3</sub>, δ): 1.03-2.14 (12H, m), 2.49 (1H, br s),  
2.68 (1H, d, J=10.8Hz), 3.32 (1H, d, J=16.5Hz),  
3.80 (3H, s), 3.64-3.96 (2H, m), 6.88 (1H, d,  
J=8.8Hz), 7.01-7.39 (11H, m), 7.56 (1H, d,  
J=2.7Hz)

MASS (APCI): 563 (M+H)<sup>+</sup>

Dihydrochloride of the above compound

MASS (APCI): 563 (M+H)<sup>+</sup> (free)

(56) (3RS,4aSR,8aRS)-3-Benzhydryl-1-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-decahydroquinoxaline

NMR (CDCl<sub>3</sub>, δ): 1.13-2.20 (11H, m), 2.67-2.85 (2H, m),  
2.90-3.33 (1H, m), 3.26 (1H, d, J=15.9Hz), 3.82  
(3H, s), 3.87 (2H, br s), 6.89 (1H, d, J=8.8Hz),  
7.00-7.34 (11H, m), 7.59 (1H, d, J=2.7Hz)

MASS (APCI): 563 (M+H)<sup>+</sup>

#### Example 4

Sodium triacetoxymethylborohydride (146 mg) was added

portionwise to a mixture of 37% aqueous formaldehyde (30

mg) and 3-benzhydryl-1-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]piperazine dihydrochloride in a mixture of dichloromethane (4 ml) and methanol (2 drops) at 0°C and the whole was stirred at 5°C ~ room temperature overnight. The mixture was partitioned between ethyl acetate and 2N sodium hydroxide. The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (60:1). The fractions containing the objective compound were collected and evaporated under reduced pressure and treated with 4N hydrogen chloride in ethyl acetate solution to give 2-benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1-methylpiperazine dihydrochloride (32.9 mg) as a colorless powder.

NMR (DMSO-d<sub>6</sub>, δ): 2.28-4.73 (16H, m), 7.15-7.40 (9H, m),  
7.55 (2H, m), 7.71 (2H, m)

MASS (APCI): 523 (M+H)<sup>+</sup> (free)

20

#### Example 5

The following compounds were obtained according to a similar manner to that of Example 4.

(1) (2S)-2-Benzhydryl-4-(2-methoxybenzyl)-1-methylpiperazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.66-4.78 (16H, m), 6.89-6.99 (2H, m),  
7.26-7.55 (12H, m)

MASS (APCI): 387 (M+H)<sup>+</sup> (free)

30

(2) (2S)-2-Benzhydryl-4-benzyl-1-methylpiperazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.60-4.91 (14H, m), 7.23-7.56 (15H, m)

MASS (APCI): 357 (M+H)<sup>+</sup> (free)

35

- (3) (6R,9aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-8-methyloctahydropyrazino[1,2-a]pyrazine trihydrochloride  
5 NMR (DMSO-d<sub>6</sub>, δ): 1.20-4.58 (21H, m), 7.23-7.32 (11H, m), 7.78 (2H, m)  
MASS (APCI): 578 (M+H)<sup>+</sup> (free)
- 10 (4) (2RS,4aSR,8aSR)-2-Benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1-methyldecahydroquinoxaline  
NMR (CDCl<sub>3</sub>, δ): 1.04-2.52 (12H, m), 3.25 (1H, d, J=15.8Hz), 3.60-4.01 (3H, m), 3.81 (3H, s), 6.85-  
15 7.51 (13H, m)  
MASS (APCI): 577 (M+H)<sup>+</sup>
- Dihydrochloride of the above compound  
MASS (APCI): 577 (M+H)<sup>+</sup> (free)
- 20 (5) (2RS,4aRS,8aSR)-2-Benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1-methyldecahydroquinoxaline  
NMR (CDCl<sub>3</sub>, δ): 1.17-2.50 (11H, m), 2.49 (3H, s), 2.70  
25 (1H, br d, J=11.2Hz), 2.83 (1H, br s), 3.09 (1H, d, J=15.3Hz), 3.79 (3H, s), 3.83-3.96 (2H, m),  
6.85 (1H, d, J=8.3Hz), 6.91-7.34 (11H, m), 7.34 (1H, d, J=2.6Hz)  
MASS (APCI): 577 (M+H)<sup>+</sup>
- 30 Dihydrochloride of the above compound  
MASS (APCI): 577 (M+H)<sup>+</sup> (free)

#### Example 6

35 The following compounds were obtained according to a

similar manner to that of Preparation 13.

(1) 6-Benzhydryl-4-benzylpiperazin-2-one

5 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.40 (2H, d,  $J=3.6\text{Hz}$ ), 2.83 (1H, d,  $J=16.4\text{Hz}$ ), 3.09 (1H, d,  $J=16.4\text{Hz}$ ), 3.29 (1H, d,  $J=13.0\text{Hz}$ ), 3.54 (1H, d,  $J=13.0\text{Hz}$ ), 4.20 (2H, m), 6.80 (1H, m), 7.08-7.45 (15H, m)

MASS (APCI): 357 (M+H)<sup>+</sup>

10 (2) 6-Benzhydryl-4-[2-methoxy-5-(trifluoromethoxy)benzyl]-piperazin-2-one

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.39 (2H, m), 2.94 (1H, d,  $J=16.3\text{Hz}$ ), 3.12 (1H, d,  $J=16.3\text{Hz}$ ), 3.40 (1H, d,  $J=13.8\text{Hz}$ ), 3.49 (1H, d,  $J=13.8\text{Hz}$ ), 3.72 (3H, s), 4.08 (1H, d,  $J=10.7\text{Hz}$ ), 4.29 (1H, m), 6.74 (1H, m), 7.00-7.43 (13H, m)

MASS (APCI): 471 (M+H)<sup>+</sup>

Example 7

20 6-Benzhydryl-4-(2-methoxy-5-trifluoromethoxy)-benzylpiperazin-2-one (47 mg) was treated with 4N hydrogen chloride in ethyl ester to give colorless powder of 6-benzhydryl-4-[2-methoxy-5-(trifluoromethoxy)benzyl]-piperazin-2-one hydrochloride (50.7 mg).

25 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.87-4.66 (12H, m), 7.05-7.57 (13H, m)

MASS (APCI): 471 (M+H)<sup>+</sup> (free)

Example 8

30 Sodium hydride (60% in mineral oil, 5 mg) was added by small portions to an ice-cooled solution of 6-benzhydryl-4-[2-methoxy-5-(trifluoromethoxy)benzyl]piperazin-2-one (30 mg) in N,N-dimethylformamide (2 ml) below 5°C under nitrogen atmosphere. After the mixture was stirred for 5 minutes, 35 methyl iodide (18.1 mg) was added to the mixture. The

whole was stirred at room temperature for 2 hours and thereto water was added. The whole was extracted with ethyl acetate. The extract was dried over magnesium sulfate and evaporated under reduced pressure. The residue  
5 was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (60:1). The fractions containing the objective compound were collected, evaporated under reduced pressure and treated with 4N  
hydrogen chloride in ethyl acetate solution to give 6-  
10 benzhydryl-4-[2-methoxy-5-(trifluoromethoxy)benzyl]-1-methylpiperazin-2-one hydrochloride (21 mg) as a colorless powder.

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.19-4.80 (12H, m), 6.97-7.79 (13H, m)

15 MASS (APCI): 485 (M+H)<sup>+</sup> (free)

#### Example 9

Aminoacetaldehyde diethyl acetal (72.4 ml) was added portionwise to a mixture of 6-benzhydryl-4-[2-methoxy-5-  
20 (trifluoromethoxy)benzyl]piperazin-2-one (78 mg) and titanium tetrachloride (1.0M in toluene, 0.033 ml) in mesitylene (5 ml) at 150°C and the whole was stirred at 160°C for 72 hours. The mixture was partitioned between ethyl acetate and 2N sodium hydroxide. The organic layer  
25 was separated, washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (90:1). The fractions containing the objective compound  
30 were collected, evaporated under reduced pressure and treated with 4N hydrogen chloride in ethyl acetate solution to give 5-benzhydryl-7-[2-methoxy-5-(trifluoromethoxy)benzyl]-5,6,7,8-tetrahydroimidazo[1,2-  
a]pyrazine dihydrochloride (74 mg) as a colorless powder.

35 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.79 (2H, m), 3.25-3.83 (6H, m), 4.39

(2H, m), 5.42 (1H, m), 6.21 (1H, s), 6.99-7.36  
(14H, m)

MASS (APCI): 494 (M+H)<sup>+</sup> (free)

5 Example 10

The following compound was obtained according to a similar manner to that of Example 9.

5-Benzhydryl-7-benzyl-5,6,7,8-tetrahydroimidazo-  
10 [1,2-a]pyrazine

MASS (APCI): 380 (M+H)<sup>+</sup>

Example 11

Lithium aluminum hydride (198 mg) was added by small  
15 portions to an ice-cooled solution of 1,4-dibenzyl-3-benzhydryl-2,5-piperazinedione (800 mg) in tetrahydrofuran (8 ml) under nitrogen atmosphere, and the mixture was stirred under reflux for 5 hours. After being cooled with ice, 2N sodium hydroxide (1 ml) was added to the mixture  
20 under nitrogen atmosphere. The resulting precipitates were filtered off and washed with tetrahydrofuran, and the filtrate and the washings were combined and evaporated under reduced pressure to give a crude oil. The oil was purified by column chromatography on silica gel using a  
25 mixed solvent of hexane and ethyl acetate (9:1). The fractions containing the objective compound were collected, evaporated under reduced pressure and treated with 4N hydrogen chloride in ethyl acetate solution to give 1,4-dibenzyl-2-benzhydrylpiperazine dihydrochloride (846 mg) as  
30 a colorless powder.

NMR (DMSO-d<sub>6</sub>, δ): 2.30-6.50 (12H, m), 7.03-7.98 (20H, m)

MASS (APCI): 433 (M+H)<sup>+</sup> (free)

35 Example 12

The following compounds were obtained according to a similar manner to that of Example 11.

- (1) (3S)-3-Benzhydryl-1-(2-methoxybenzyl)piperazine  
5 dihydrochloride  
NMR (DMSO- $d_6$ ,  $\delta$ ): 2.60-4.71 (14H, m), 6.92-7.03 (2H, m),  
7.29-7.46 (12H, m)  
MASS (APCI): 373 (M+H)<sup>+</sup> (free)
- 10 (2) (3S)-3-Benzhydryl-1-benzylpiperazine dihydrochloride  
NMR (DMSO- $d_6$ ,  $\delta$ ): 3.00-4.75 (11H, m), 7.26-7.52 (15H,  
m)  
MASS (APCI): 343 (M+H)<sup>+</sup> (free)

15 Example 13

A solution of [2-[[ (4R,8aS)-4-benzhydrylhexahydropyrrolo[1,2-a]pyrazin-2-yl]methyl]-4-[5-(trifluoromethyl)-1H-tetrazol-1-yl]phenoxy]acetic acid  
methyl ester in methanol containing 20% ammonia was stored  
20 at room temperature for 1 day. The mixture was evaporated  
under reduced pressure. The residue was purified by column  
chromatography on silica gel using a mixed solvent of  
dichloromethane and methanol (100:1). The fractions  
containing the objective compound were collected and  
25 evaporated under reduced pressure. The residue was treated  
with 4N hydrogen chloride in ethyl acetate to give  
colorless powders of 2-[2-[[ (4R,8aS)-4-benzhydrylhexahydropyrrolo[1,2-a]pyrazin-2-yl]methyl]-4-[5-(trifluoromethyl)-1H-tetrazol-1-yl]phenoxy]acetamide  
30 dihydrochloride (70 mg).

IR (KBr): 3400, 1681, 1504  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.40-5.10 (17H, m), 4.60 (2H, s),  
7.16-7.80 (13H, m)

MASS (APCI): 592 (M+H)<sup>+</sup> (free)



Example 14

(4R,8aS)-4-Benzhydryl-2-(2-methoxy-5-bromobenzyl)-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride (29.8 mg)  
was dissolved in a mixture of 1,2-dimethoxyethane (0.5 ml)  
5 and 2M aqueous sodium carbonate (0.16 ml). Then  
phenylboronic acid (9.01 mg) and  
tetrakis(triphenylphosphine)palladium (6.1 mg) were added  
to the solution at room temperature. The whole was stirred  
for 2 hours at 85°C. The reaction mixture was poured into  
10 water, extracted with ethyl acetate. The extract was  
washed with brine, dried over magnesium sulfate and  
evaporated under reduced pressure. The resulting residue  
was purified by preparative TLC (0.5 mm) with a mixture of  
dichloromethane and methanol (15:1) as an eluent, and  
15 treated with 4N hydrogen chloride in ethyl acetate to give  
(4R,8aS)-4-benzhydryl-2-[(4-methoxy-[1,1'-biphenyl]-3-  
yl)methyl]octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
(24.4 mg) as a brownish power.  
NMR (DMSO-d<sub>6</sub>, δ): 1.50-2.20 (3H, m), 2.70-4.50 (17H, m),  
20 6.72-7.80 (18H, m)  
MASS (APCI): 489 (M+H)<sup>+</sup> (free)

Example 15

The following compound was obtained according to a  
25 similar manner to that of Example 14.

(4R,8aS)-4-Benzhydryl-2-[2-methoxy-5-(3-thienyl)-  
benzyl]octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.60-2.15 (3H, m), 2.70-4.60 (17H, m),  
30 6.99-7.90 (16H, m)  
MASS (APCI): 495 (M+H)<sup>+</sup> (free)

Example 16

(4R,8aS)-4-Benzhydryl-2-(2-methoxy-5-bromobenzyl)-  
35 octahydropyrrolo[1,2-a]pyrazine dihydrochloride (29.8 mg)

was dissolved in N,N-dimethylformamide (2.0 ml). Then potassium carbonate (85.6 mg), N-methylimidazol (43.6 mg), palladium acetate (3.98 mg) and triphenylphosphine (9.29 mg) were added to the solution at room temperature. The whole was stirred for 10 hours at 140°C. The reaction mixture was poured into aqueous sodium hydrogen carbonate. The whole mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The resulting residue was purified by preparative TLC (0.5 mm) with a mixture of dichloromethane and methanol (10:1) as an eluent, and treated with 4N hydrogen chloride in ethyl acetate to give (4R,8aS)-4-benzhydryl-2-[2-methoxy-5-(3-methyl-3H-imidazol-4-yl)benzyl]octahydropyrrolo[1,2-a]pyrazine dihydrochloride (46.1 mg) as a colorless powder.

NMR (DMSO-d<sub>6</sub>, δ): 1.50-2.10 (3H, m), 1.91 (3H, s), 26.0-4.50 (13H, m), 4.01 (3H, s), 7.11-7.80 (14H, m), 9.21 (1H, s)

MASS (APCI): 493 (M+H)<sup>+</sup> (free)

20

#### Example 17

The following compound was obtained according to a similar manner to that of Preparation 18.

(4R,9aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrido[1,2-a]pyrazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.23-1.90 (3H, m), 2.65-4.74 (16H, m), 3.73 (3H, s), 7.19-7.73 (13H, m)

MASS (APCI): 563 (M+H)<sup>+</sup> (free)

30

#### Example 18

(2R)-2-Benzylloxycarbonylamino-3-[N-(2-methoxybenzyl)-N-(2-oxo-3,3-diphenylpropyl)amino]propionic acid methyl ester (1.55 g) was dissolved in a mixture of

35

tetrahydrofuran (50 ml) and triethylamine (0.744 ml), and the whole was hydrogenated over 10% palladium - charcoal (50% wet, 0.15 g) at room temperature under atmospheric pressure for 4 hours. After removal of the catalyst by  
5 filtration, the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (2:1) as an eluent. The fractions containing the objective compound were collected and  
10 evaporated under reduced pressure to give (2R)-6-benzhydryl-4-(2-methoxybenzyl)piperazine-2-carboxylic acid methyl ester (663.8 mg) as a yellow oil.

NMR (CDCl<sub>3</sub> δ): 1.91 (1H, dd, J=10.9, 11.0Hz), 2.13 (1H, d, J=10.9Hz), 2.71 (1H, d, J=10.9Hz), 3.15 (1H, d, J=10.9Hz), 3.48-3.86 (6H, m), 3.62 (3H, s), 3.70 (3H, s), 6.78-7.50 (14H, m)

MASS (APCI): 431 (M+H)<sup>+</sup>

#### Example 19

20 The following compound was obtained according to a similar manner to that of Preparation 26.

[(2R)-6-Benzhydryl-4-(2-methoxybenzyl)piperazin-2-yl]methanol dihydrochloride

25 NMR (DMSO-d<sub>6</sub>, δ): 2.80-4.80 (16H, m), 2.69-7.43 (14H, m)

MASS (APCI): 403 (M+H)<sup>+</sup> (free)

#### Example 20

30 Potassium carbonate (81.3 mg) was added to a mixture of [(2R)-6-benzhydryl-4-(2-methoxybenzyl)piperazin-2-yl]methanol dihydrochloride (48.0 mg) in a mixed solvent of dichloromethane and water. Chloroacetyl chloride was added to the mixture below 5°C and the whole was stirred for 1  
35 hour. The organic layer was separated, washed with brine,

dried over magnesium sulfate, and evaporated under reduced pressure. The resulting residue was dissolved into tert-butanol (4 ml) and potassium tert-butoxide (22.0 mg) was added to the mixture. The reaction mixture was poured into  
5 aqueous sodium hydrogen carbonate, and the whole was extracted with ethyl acetate. The extract was dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by preparative TLC (15 PLC plate 20 x 20 cm, silica gel 60 F<sub>254</sub>, 1 mm, Merck) with a mixture  
10 of hexane and ethyl acetate as an eluent to give (9aR)-6-benzhydryl-8-(2-methoxybenzyl)hexahydropyrazino[2,1-c]-[1,4]oxazin-4-one (30 mg) as a colorless oil.

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.38 (1H, d, J=9.7Hz), 2.48 (1H, d, J=10.9Hz), 2.68 (1H, d, J=10.9Hz), 2.83 (1H, d, J=9.7Hz), 3.47-4.17 (8H, m), 3.73 (3H, s), 5.37  
15 (1H, d, J=12.3Hz), 6.78-7.32 (14H, m)

MASS (APCI): 443 (M+H)<sup>+</sup> (free)

#### Example 21

20 Lithium aluminum hydride (3.9 mg) was added to an ice-cooled solution of (9aR)-6-benzhydryl-8-(2-methoxybenzyl)-hexahydropyrazino[2,1-c][1,4]oxazin-4-one (22.9 mg) in tetrahydrofuran (1.1 ml) under nitrogen atmosphere. The mixture was stirred for 3 hours below 5°C. The reaction  
25 mixture was allowed to room temperature and stirred for 2 hours. After addition of another lithium aluminum hydride (4 mg), the reaction mixture was stirred for 14 hours. The reaction was quenched by a sequential addition of water (0.12 ml), 15% aqueous sodium hydroxide (0.12 ml) and water  
30 (0.36 ml), and the whole was stirred at room temperature for 1 hour. The insoluble materials were removed by filtration. The filtrate was dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by preparative TLC (0.5 mm) with a mixture of  
35 hexane and ethyl acetate (1:1) as an eluent. The resulting

residue was treated with 4N hydrogen chloride in ethyl acetate to give (9aR)-6-benzhydryl-8-(2-methoxybenzyl)hexahydropyrazino-[1,2-c][1,4]oxazine dihydrochloride (9.6 mg) as a brownish powder.

- 5        NMR (DMSO- $d_6$ ,  $\delta$ ): 0.83-1.27 (1H, m), 2.60-4.30 (16H, m),  
         3.71 (3H, s), 6.92-7.44 (14H, m)  
         MASS (APCI): 493 (M+H)<sup>+</sup> (free)

Example 22

- 10        (6R, 9aR)-6-Benzhydryl-8-(tert-butoxycarbonyl)-  
         octahydropyrazino[2,1-c][1,4]oxazine was treated with 4N  
         hydrogen chloride in 1,4-dioxane to give (6R, 9aR)-  
         octahydro-6-benzhydrylpyrazino[2,1-c][1,4]oxazine  
         dihydrochloride as a yellowish powder. (6R, 9aR)-6-  
15    Benzhydryl-8-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-  
         1-yl]benzyl]octahydropyrazino[2,1-c][1,4]oxazine  
         dihydrochloride was obtained from (6R, 9aR)-6-  
         benzhydrylhexahydropyrazino[2,1-c][1,4]oxazine  
         dihydrochloride according to a similar manner to that of  
20    Example 2.  
         NMR (DMSO- $d_6$ ,  $\delta$ ): 2.07-2.60 (3H, m), 2.75-4.54 (17H, m),  
         7.18-7.78 (13H, m)  
         MASS (APCI): 565 (M+H)<sup>+</sup> (free)

25    Example 23

- 4N Hydrogen chloride in ethyl acetate solution (3 ml)  
         was added to a solution of (2R)-2-[[N-(2-methoxybenzyl)-N-  
         (2-oxo-3,3-diphenylpropyl)amino]methyl]piperazine-1,4-  
         dicarboxylic acid 4-benzyl ester 1-tert-butyl ester (160  
30    mg) in ethyl acetate (3 ml) at room temperature. After  
         being stirred for 2 hours, the reaction mixture was  
         concentrated under reduced pressure. The resulting residue  
         was dissolved into dichloromethane (4 ml). Sodium  
         triacetoxyborohydride (150 mg) was added to the stirred  
35    mixture and the whole was stirred at room temperature for

18 hours. The mixture was partitioned between ethyl acetate and 2N sodium hydroxide. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The resulting  
5 residue was purified by column chromatography on silica gel using a mixed solvent of hexane and ethyl acetate (3:4) as an eluent to give (6R,9aR)-6-benzhydryl-8-(2-methoxybenzyl)octahydropyrazino[1,2-a]pyrazine-2-carboxylic acid benzyl ester (108 mg) as a colorless powder.

10 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.83-2.09 (3H, m), 2.43 (2H, m), 2.60-3.05 (4H, m), 3.20-3.56 (3H, m), 3.68 (3H, s), 3.78 (2H, m), 4.18 (1H, d, J=6.9Hz), 5.08 (2H, s), 6.70-7.32 (19H, m)

MASS (APCI): 562 (M+H)<sup>+</sup>

15

Example 24

A solution of (6R,9aR)-6-benzhydryl-8-(2-methoxybenzyl)octahydropyrazino[1,2-a]pyrazine-2-carboxylic acid benzyl ester (100 mg) and triethylamine (0.049 ml) in  
20 tetrahydrofuran (3 ml) was hydrogenated over 10% palladium-carbon (50% wet, 20 mg) at room temperature under atmospheric pressure for 2 hours. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure to give an oil, which was purified by  
25 column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (4:1). The fractions containing the objective compound were collected and evaporated under reduced pressure and the resulting residue was treated with 4N hydrogen chloride in ethyl acetate to  
30 give (6R,9aS)-4-benzhydryl-2-(2-methoxybenzyl)-octahydropyrazino[1,2-a]-pyrazine trihydrochloride (58 mg) as a colorless powder.

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.26-4.45 (19H, m), 6.91-7.46 (14H, m)

35 MASS (APCI): 428 (M+H)<sup>+</sup> (free)

Example 25

Acetyl chloride (3 drops) was added to a mixture of (6R,9aS)-4-benzhydryl-2-(2-methoxybenzyl)octahydropyrazino-  
5 [1,2-a]pyrazine trihydrochloride (20 mg) and N,N-diisopropylethylamine (6 drops) in dichloromethane (1 ml) under ice-cooling. After being stirred at the same temperature for 2 hours, the mixture was poured into ice-water and extracted with ethyl acetate. The extract was  
10 washed with brine, dried over sodium sulfate and evaporated under reduced pressure to give a crude oil. The oil was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (50:1) as an eluent. The fractions containing the objective compound  
15 were collected and evaporated under reduced pressure and the resulting residue was treated with 4N hydrogen chloride in ethyl acetate to give 1-[(6R,9aR)-6-benzhydryl-8-(2-methoxybenzyl)octahydropyrazino[1,2-a]pyrazin-2-yl]ethanone dihydrochloride (9.8 mg) as a colorless powder.

20 NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.90-4.60 (21H, m), 6.95-7.39 (14H, m)

MASS (APCI): 470 (M+H)<sup>+</sup> (free)

Example 26

25 1-Chloroethyl chloroformate (0.055 ml) was added to a stirred solution of (6R,9aR)-6-benzhydryl-8-(2-methoxybenzyl)octahydropyrazino[1,2-a]pyrazine-2-carboxylic acid benzyl ester (140 mg) in 1,2-dichloroethane (3 ml) under nitrogen atmosphere. After being stirred for 2.5  
30 hours at 50°C, the whole mixture was concentrated under reduced pressure. The resulting residue was dissolved into methanol (5 ml) and the reaction mixture was stirred for 1.5 hours under reflux. The mixture was concentrated under reduced pressure to give an oily residue. Sodium  
35 triacetoxyborohydride (424 mg) and N,N-

diisopropylethylamine (0.087 ml) were added to a mixture of the residue obtained in the above procedure and 2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzaldehyde (75 mg) in dichloromethane (6 ml), and the whole was stirred at room temperature for 18 hours. The resulting mixture was partitioned between ethyl acetate and 2N sodium hydroxide. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (50:1) as an eluent to give (6R,9aR)-6-benzhydryl-8-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrazino[1,2-a]pyrazine-2-carboxylic acid benzyl ester (155 mg) as a colorless powder.

NMR (CDCl<sub>3</sub>, δ): 1.83-2.11 (3H, m), 2.44 (2H, m), 2.62-3.05 (4H, m), 3.21-3.90 (8H, m), 4.18 (1H, d, J=7.0Hz), 5.08 (2H, s), 6.90-7.78 (18H, m)  
MASS (APCI): 698 (M+H)<sup>+</sup>

20

#### Example 27

The following compound was obtained according to a similar manner to that of Example 24.

(6R,9aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-octahydropyrazino[1,2-a]pyrazine trihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 2.10-4.47 (19H, m), 7.24-7.34 (11H, m), 7.79-7.85 (2H, m)

MASS (APCI): 564 (M+H)<sup>+</sup> (free)

#### Example 28

Methyl chloroformate (3 drops) was added to a mixture of (6R,9aS)-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-



octahydropyrazino[1,2-a]pyrazine trihydrochloride (12 mg) and N,N-diisopropylethylamine (6 drops) in dichloromethane (1 ml) under ice-cooling. After being stirred at the same temperature for 2 hours, the mixture  
5 was poured into ice-water and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The resulting oil was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and  
10 methanol (50:1) as an eluent. The fractions containing the objective compound were collected and evaporated under reduced pressure and the resulting residue was treated with 4N hydrogen chloride in ethyl acetate to give (6R,9aR)-6-benzhydryl-8-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-  
15 1-yl]benzyl]octahydropyrazino[1,2-a]pyrazine-2-carboxylic acid methyl ester dihydrochloride (7.0 mg) as a colorless powder.

NMR (DMSO-d<sub>6</sub>, δ): 2.10-4.45 (21H, m), 7.18-7.78 (13H, m)  
20 MASS (APCI): 622 (M+H)<sup>+</sup> (free)

#### Example 29

The following compound was obtained according to a similar manner to that of Example 25.

25

1-[(6R,9aR)-6-Benzhydryl-8-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-octahydropyrazino[1,2-a]pyrazin-2-yl]ethanone dihydrochloride

30 NMR (DMSO-d<sub>6</sub>, δ): 1.90-4.40 (21H, m), 7.21-7.37 (11H, m), 7.78 (2H, m)  
MASS (APCI): 606 (M+H)<sup>+</sup> (free)

#### Example 30

35 A 1M solution of sodium triacetoxyborohydride in N,N-

dimethylformamide (75  $\mu$ l) was added portionwise to a mixture of 2-methoxybenzaldehyde (7.5 mg) and a solution of 2-benzhydryl-1-methylpiperazine dihydrochloride (17.0 mg) in N,N-dimethylformamide (50  $\mu$ l) at 0°C and the whole was  
5 stirred at 0°C to 5°C for 1 hour and further at 5°C to room temperature for 1 hour. The mixture was extracted with aqueous 0.25N sulfuric acid solution and washed with ethyl acetate. The combined solution was applied on solid phase extraction column cartridge (C18, 200 mg) and eluted with  
10 water and acetonitrile successively. The eluate was concentrated in vacuo to give 2-benzhydryl-4-(2-methoxybenzyl)-1-methylpiperazine (14.3 mg).

MASS (APCI): 387 (M+H)<sup>+</sup>

15 Example 31

The following compounds were obtained according to a similar manner to that of Example 30.

(1) 2-Benzhydryl-4-(2,6-dimethoxybenzyl)-1-methylpiperazine  
20

MASS (APCI): 417 (M+H)<sup>+</sup>

(2) 2-Benzhydryl-4-(2,4-dimethoxybenzyl)-1-methylpiperazine  
25

MASS (APCI): 417 (M+H)<sup>+</sup>

(3) 2-Benzhydryl-4-[[2,2-difluorobenzo[1,3]dioxol-4-yl)methyl]-1-methylpiperazine  
30

MASS (APCI): 437 (M+H)<sup>+</sup>

(4) 2-Benzhydryl-4-(2,4,6-trimethoxybenzyl)-1-methylpiperazine  
35

MASS (APCI): 447 (M+H)<sup>+</sup>

(5) 2-Benzhydryl-4-(2,4,5-trimethoxybenzyl)-1-

methylpiperazine

MASS (APCI): 447 (M+H)<sup>+</sup>

5 (6) 2-Benzhydryl-4-[2-methoxy-5-(1H-tetrazol-1-yl)benzyl]-  
1-methylpiperazine

MASS (APCI): 455 (M+H)<sup>+</sup>

10 (7) 2-Benzhydryl-4-[2-methoxy-5-(trifluoromethyl)benzyl]-  
1-methylpiperazine

MASS (APCI): 455 (M+H)<sup>+</sup>

15 (8) 2-Benzhydryl-4-[2-methoxy-5-(trifluoromethoxy)benzyl]-  
1-methylpiperazine

MASS (APCI): 471 (M+H)<sup>+</sup>

(9) 2-Benzhydryl-4-(5-bromo-2,4-dimethoxybenzyl)-1-  
methylpiperazine

MASS (APCI): 497 (M+H)<sup>+</sup>

20 (10) 2-Benzhydryl-4-(5-bromo-2-methoxybenzyl)-1-  
methylpiperazine ditrifluoroacetate

MASS (APCI): 467 (M+H)<sup>+</sup>

25 (11) 2-Benzhydryl-4-[5-(1-methylethyl)-2-methoxybenzyl]-1-  
methylpiperazine

MASS (APCI): 429 (M+H)<sup>+</sup>

(12) 2-Benzhydryl-4-(2,4-dimethoxy-5-methylbenzyl)-1-  
methylpiperazine

30 MASS (APCI): 431 (M+H)<sup>+</sup>

(13) 2-Benzhydryl-4-(2-ethoxybenzyl)-1-methylpiperazine

MASS (APCI): 401 (M+H)<sup>+</sup>

35 (14) 2-Benzhydryl-4-[2-(benzyloxy)benzyl]-1-

- methylnpiperazine  
MASS (APCI): 463 (M+H)<sup>+</sup>
- 5 (15) 2-Benzhydryl-4-[2-(allyloxy)benzyl]-1-methylnpiperazine  
MASS (APCI): 413 (M+H)<sup>+</sup>
- (16) 2-Benzhydryl-4-(2-cyanobenzyl)-1-methylnpiperazine  
MASS (APCI): 382 (M+H)<sup>+</sup>
- 10 (17) 2-Benzhydryl-4-(2-methoxycarbonylbenzyl)-1-  
methylnpiperazine  
MASS (APCI): 415 (M+H)<sup>+</sup>
- (18) 2-Benzhydryl-4-(2-iodobenzyl)-1-methylnpiperazine  
15 MASS (APCI): 483 (M+H)<sup>+</sup>
- (19) 2-Benzhydryl-4-(2-nitrobenzyl)-1-methylnpiperazine  
MASS (APCI): 402 (M+H)<sup>+</sup>
- 20 (20) 2-Benzhydryl-4-(2-bromobenzyl)-1-methylnpiperazine  
MASS (APCI): 437 (M+H)<sup>+</sup>
- (21) 2-Benzhydryl-4-[2-(trifluoromethyl)benzyl]-1-  
methylnpiperazine  
25 MASS (APCI): 425 (M+H)<sup>+</sup>
- (22) 2-Benzhydryl-4-(2,5-dimethylbenzyl)-1-methylnpiperazine  
MASS (APCI): 416 (M+H)<sup>+</sup>
- 30 (23) 2-Benzhydryl-4-(4-dimethylamino-2-methoxybenzyl)-1-  
methylnpiperazine  
MASS (APCI): 429 (M+H)<sup>+</sup>
- 35 (24) 2-Benzhydryl-4-[(2-methoxynaphthalen-1-yl)methyl]-1-  
methylnpiperazine

MASS (APCI): 436 (M+H)<sup>+</sup>

(25) 2-Benzhydryl-4-[(4-methoxypyridin-3-yl)methyl]-1-methylpiperazine

5 MASS (APCI): 387 (M+H)<sup>+</sup>

(26) 2-Benzhydryl-4-[2-(difluoromethoxy)benzyl]-1-methylpiperazine

10 MASS (APCI): 422 (M+H)<sup>+</sup>

(27) 2-Benzhydryl-4-[2-(trifluoromethoxy)benzyl]-1-methylpiperazine

MASS (APCI): 441 (M+H)<sup>+</sup>

15 (28) 2-Benzhydryl-4-[2-(chlorobenzyl)-1-methylpiperazine

MASS (APCI): 390 (M+H)<sup>+</sup>

### Example 32

20 A 1M solution of sodium triacetoxyborohydride in N,N-dimethylformamide (75  $\mu$ l) was added portionwise to a mixture of 2-chloro-6-methoxybenzaldehyde (9.4 mg) and a solution of (4R,8aS)-4-benzhydryloctahydropyrrolo[1,2-a]pyrazine dihydrochloride (18.3 mg) in N,N-dimethylformamide (50  $\mu$ l) at 25°C and the whole was stirred  
25 at room temperature for 2 hours. The mixture was purified by high pressure liquid chromatography eluting with aqueous 0.1% trifluoroacetic acid solution-acetonitrile (90:10→10:90). The solution was concentrated in vacuo. To the residue was added ethyl acetate and aqueous 5%  
30 potassium carbonate solution. The mixture was applied on liquid/liquid extraction cartridge (CE1000M, VARIAN) and eluted with ethyl acetate. The eluate was concentrated in vacuo to give (4R,8aS)-4-benzhydryl-2-(2-chloro-6-methoxybenzyl)octahydropyrrolo-  
35 [1,2-a]pyrazine (11.0 mg).

MASS (APCI): 447 (M+H)<sup>+</sup>

Example 33

The following compounds were obtained according to a  
5 similar manner to that of Example 32.

(1) (4R,8aS)-4-Benzhydryl-2-[2-methoxy-6-(trifluoromethyl)benzyl]octahydropyrrolo[1,2-a]pyrazine

10 MASS (APCI): 481 (M+H)<sup>+</sup>

(2) (4R,8aS)-4-Benzhydryl-2-[2,4-dimethoxy-6-(methoxycarbonyl)benzyl]octahydropyrrolo[1,2-a]pyrazine

15 MASS (APCI): 501 (M+H)<sup>+</sup>

(3) (4R,8aS)-4-Benzhydryl-2-(2,4,6-trimethylbenzyl)-octahydropyrrolo[1,2-a]pyrazine

20 MASS (APCI): 425 (M+H)<sup>+</sup>

(4) (4R,8aS)-4-Benzhydryl-2-(2,3,6-trifluorobenzyl)-octahydropyrrolo[1,2-a]pyrazine

MASS (APCI): 414 (M+H)<sup>+</sup>

25 (5) (4R,8aS)-4-Benzhydryl-2-[(3-methoxypyridin-2-yl)methyl]octahydropyrrolo[1,2-a]pyrazine

MASS (APCI): 414 (M+H)<sup>+</sup>

30 (6) (4R,8aS)-4-Benzhydryl-2-(2,5-dimethoxybenzyl)-octahydropyrrolo[1,2-a]pyrazine

MASS (APCI): 443 (M+H)<sup>+</sup>

(7) (4R,8aS)-4-Benzhydryl-2-(4-dimethylamino-2-methoxybenzyl)octahydropyrrolo[1,2-a]pyrazine

35 MASS (APCI): 180 (M+H)<sup>+</sup>

- (8) (4R, 8aS)-4-Benzhydryl-2-(2-methoxynaphthalen-1-ylmethyl)octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 463 (M+H)<sup>+</sup>
- 5
- (9) (4R, 8aS)-4-Benzhydryl-2-[2-(difluoromethoxy)benzyl]-octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 449 (M+H)<sup>+</sup>
- 10
- (10) (4R, 8aS)-4-Benzhydryl-2-[2-(trifluoromethoxy)benzyl]-octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 467 (M+H)<sup>+</sup>
- 15
- (11) (4R, 8aS)-4-Benzhydryl-2-(3,5-dimethoxybenzyl)-octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 443 (M+H)<sup>+</sup>
- 20
- (12) (4R, 8aS)-4-Benzhydryl-2-[2,3-(methylenedioxy)benzyl]-octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 427 (M+H)<sup>+</sup>
- 25
- (13) (4R, 8aS)-4-Benzhydryl-2-[(4-(methoxypyridin-3-yl)methyl)octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 414 (M+H)<sup>+</sup>
- 30
- (14) (4R, 8aS)-4-Benzhydryl-2-(2-methoxybenzyl)-octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 413 (M+H)<sup>+</sup>
- 35
- (15) (4R, 8aS)-4-Benzhydryl-2-[2-(methylthio)benzyl]-octahydropyrrolo[1,2-a]pyrazine  
MASS (APCI): 429 (M+H)<sup>+</sup>
- (16) (4R, 8aS)-4-Benzhydryl-2-(2-ethoxy-6-methoxybenzyl)-octahydropyrrolo[1,2-a]pyrazine

MASS (APCI): 457 (M+H)<sup>+</sup>

(17) (4R, 8aS)-4-Benzhydryl-2-(2-isopropoxy-6-methoxybenzyl)octahydropyrrolo[1,2-a]pyrazine

5 MASS (APCI): 471 (M+H)<sup>+</sup>

(18) (4R, 8aS)-4-Benzhydryl-2-(2-methoxy-6-propoxybenzyl)octahydropyrrolo[1,2-a]pyrazine

MASS (APCI): 471 (M+H)<sup>+</sup>

10

(19) (4R, 8aS)-4-Benzhydryl-2-[2-methoxy-6-(2-methoxyethoxy)benzyl]octahydropyrrolo[1,2-a]pyrazine

MASS (APCI): 487 (M+H)<sup>+</sup>

15 (20) (4R, 8aS)-4-Benzhydryl-2-[2-methoxy-6-(2,2,2-trifluoroethoxy)benzyl]octahydropyrrolo[1,2-a]pyrazine

MASS (APCI): 511 (M+H)<sup>+</sup>

(21) (4R, 8aS)-4-Benzhydryl-2-(2-chloro-5-nitrobenzyl)octahydropyrrolo[1,2-a]pyrazine

20

MASS (APCI): 462 (M+H)<sup>+</sup>

(22) (4R, 8aS)-4-Benzhydryl-2-(2,4-dichlorobenzyl)-octahydropyrrolo[1,2-a]pyrazine

25

MASS (APCI): 541 (M+H)<sup>+</sup>

(23) (4R, 8aS)-4-Benzhydryl-2-(2-fluoro-6-methoxybenzyl)-octahydropyrrolo[1,2-a]pyrazine

MASS (APCI): 431 (M+H)<sup>+</sup>

30

(24) (4R, 8aS)-4-Benzhydryl-2-[2-(cyanomethoxy)-6-methoxybenzyl]octahydropyrrolo[1,2-a]pyrazine

MASS (APCI): 468 (M+H)<sup>+</sup>

35 Example 34



The following compounds were obtained according to a similar manner to that of Example 4.

(1) 2-Benzhydryl-1-ethyl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]piperazine dihydrochloride  
IR (KBr, FT-IR): 1454, 1320, 1270, 1230  $\text{cm}^{-1}$   
NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 2.57-5.29 (15H, m), 3.81 (3H, s), 7.00-7.86 (13H, m)  
MASS (APCI): 537 (M+H)<sup>+</sup> (free)

(2) 2-Benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1-propylpiperazine dihydrochloride  
IR (KBr, FT-IR): 1505, 1455, 1320, 1270, 1200  $\text{cm}^{-1}$   
NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 0.47-5.20 (17H, m), 3.80 (3H, s), 7.10-7.88 (13H, m)  
MASS (APCI): 551 (M+H)<sup>+</sup> (free)

### 20 Example 35

To a suspension of 2-[2-benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1-piperazinyl]acetic acid (70 mg) and triethylamine (20 mg) in dichloromethane (5 ml) was added 2-chloro-1-methylpyridinium iodide (70 mg) at room temperature. After being stirred for 30 minutes, 28% aqueous ammonia (1 drop) was added to the solution. After being stirred for 1.5 hours, the mixture was washed with water. The organic layer was separated, dried over magnesium sulfate, and evaporated under reduced pressure. The syrup was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (20:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give a syrup. The syrup was treated with 4N hydrogen chloride in ethyl

acetate (1 ml) to give 2-[2-benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1-piperazinyl]acetamide dihydrochloride (81 mg).

IR (KBr, FT-IR): 1665, 1610, 1440, 1320, 1265,  
5 1235  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.70-5.95 (14H, m), 3.66 (3H, s),  
7.10-8.10 (13H, m)

MASS (APCI): 566 (M+H)<sup>+</sup> (free)

10 Example 36

The following compounds were obtained according to a similar manner to that of Example 2 from 2-benzhydryl-1-methylpiperazine dihydrochloride.

15 (1) 2-Benzhydryl-4-(2-ethoxy-6-methoxybenzyl)-1-methylpiperazine dihydrochloride

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.50-2.10 (4H, m), 2.48 (3H, s), 3.14-  
4.60 (12H, m), 4.69-4.74 (1H, m), 5.65-5.69 (1H,  
m), 6.45-6.49 (2H, d), 7.21-7.52 (13H, m)

20 MASS (APCI): 431 (M+1) (free)

(2) 2-Benzhydryl-4-[2-ethoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1-methylpiperazine dihydrochloride

25 NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.12-5.35 (20H, m), 6.74-7.74 (13H, m)  
MASS (APCI): 537 (M+1) free

(3) 2-Benzhydryl-4-(2-isopropoxy-6-methoxybenzyl)-1-methylpiperazine dihydrochloride

30 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.10-1.30 (6H, m), 2.30-5.00 (17H, m),  
6.55-6.71 (2H, m), 7.22-7.51 (11H, m)  
MASS (APCI): 445 (M+H)<sup>+</sup> (free)

Example 37

35 The following compounds were obtained according to a

similar manner to that of Example 2 from (6R,9aR)-6-benzhydryloctahydropyrazino[2,1-c][1,4]oxazine dihydrochloride.

- 5 (1) (6R,9aR)-6-Benzhydryl-8-(2-ethoxy-6-methoxybenzyl)octahydropyrazino[2,1-c][1,4]oxazine dihydrochloride

NMR (CDCl<sub>3</sub>, δ): 2.50 (1H, br), 3.07-3.34 (3H, m), 3.65-4.27 (14H, m), 4.67-4.83 (2H, m), 5.73 (1H, m),  
10 6.47 (2H, d, J=8.5Hz), 7.17-7.78 (13H, m), 12.86 (1H, m), 14.18 (1H, m)

MASS (APCI): 473 (M+1) (free)

- 15 (2) (6R,9aR)-6-Benzhydryl-8-[2-ethoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrazino[2,1-c][1,4]oxazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.27-4.55 (22H, m), 7.17-7.79 (13H, m)

20 MASS (APCI): 579 (M+1) (free)

- (3) (6R,9aR)-6-Benzhydryl-8-(2-isopropoxy-6-methoxybenzyl)octahydropyrazino[2,1-c][1,4]oxazine dihydrochloride

25 NMR (DMSO-d<sub>6</sub>, δ): 1.10-1.30 (6H, m), 3.64 (3H, s), 2.30-4.8 (16H, m), 6.55-6.71 (2H, m), 7.22-7.51 (11H, m), 10.50-11.50 (2H, m)

MASS (APCI): 487 (M+H)<sup>+</sup> (free)

30 Example 38

A mixture of (4R,8aS)-4-benzhydryl-2-(5-bromo-2-methoxybenzyl)octahydropyrrolo[1,2-a]pyrazine dihydrochloride (100 mg), diethyl-3-pyridylboran (39.1 mg), tetrakis(triphenylphosphine)palladium (20.5 mg), powdered  
35 potassium hydroxide (29.8 mg) and tetrabutylammonium

bromide (17.1 mg) in tetrahydrofuran (2 ml) were stirred for 8 hours at 70°C. After being cooled to room temperature, the reaction mixture was poured into aqueous saturated sodium hydrogen carbonate, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The resulting residue was purified by preparative TLC (0.5 mm) with a mixture of dichloromethane and methanol (10:1) as an eluent. The resulting residue was treated with 4N hydrogen chloride in ethyl acetate to give (4R,8aS)-4-benzhydryl-2-[2-methoxy-5-(3-pyridyl)benzyl]octahydropyrrolo[1,2-a]pyrazine trihydrochloride (25.9 mg).

NMR (DMSO-d<sub>6</sub>, δ): 3.23-4.00 (20H, m), 7.12-9.14 (17H, m)

MASS (APCI): 490 (M+1) (free)

#### Example 39

The following compounds were obtained according to a similar manner to that of Example 2 from (4R,8aS)-4-benzhydryloctahydropyrrolo[1,2-a]pyrazine dihydrochloride.

(1) (4R,8aS)-4-Benzhydryl-2-[2-methoxy-5-(2-thienyl)benzyl]octahydropyrrolo[1,2-a]pyrazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ): 1.5-2.2 (5H, m), 2.55-4.99 (25H, m), 6.99-7.82 (16H, m)

MASS (APCI): 495 (M+1) (free)

(2) (4R,8aS)-4-Benzhydryl-2-[5-(3-furyl)-2-methoxybenzyl]octahydropyrrolo[1,2-a]pyrazine dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.40-4.49 (20H, m), 6.92-8.08 (16H, m)

MASS (APCI): 479 (M+1) (free)

- (3) (4R,8aS)-4-Benzhydryl-2-[2-methoxy-5-(4-pyridyl)benzyl]octahydropyrrolo[1,2-a]pyrazine trihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ): 1.64-5.14 (21H, m), 6.96-8.97 (17H, m)  
5 MASS (APCI): 490 (M+1) (free)
- (4) (4R,8aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(methylthio)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
10 NMR (DMSO-d<sub>6</sub>, δ): 1.30-4.55 (23H, m), 7.15-7.65 (13H, m)  
MASS (APCI): 527 (M+1) (free)
- (5) (4R,8aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(methylsulfonyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
15 NMR (DMSO-d<sub>6</sub>, δ): 1.70-4.55 (23H, m), 7.17-7.76 (13H, m)  
20 MASS (APCI): 559 (M+1) (free)
- (6) (4R,8aS)-4-Benzhydryl-2-(2-isopropoxy-6-methoxybenzyl)octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
25 NMR (DMSO-d<sub>6</sub>, δ): 1.10-1.30 (6H, m), 3.57 (3H, s), 2.30-4.8 (16H, m), 6.55-6.68 (2H, m), 7.22-7.51 (11H, m)  
MASS (APCI): 471 (M+H)<sup>+</sup> (free)
- (7) (4R,8aS)-4-Benzhydryl-2-[2-isopropoxy-5-(trifluoromethoxy)benzyl]octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
30 NMR (DMSO-d<sub>6</sub>, δ): 1.10-1.30 (6H, m), 2.30-4.8 (16H, m), 7.18-7.71 (13H, m)  
35 MASS (APCI) : 525 (M+H)<sup>+</sup> (free)

- (8) (4R,8aS)-4-Benzhydryl-2-[2-ethoxy-5-(trifluoromethoxy)benzyl]octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
5 NMR (DMSO-d<sub>6</sub>, δ): 1.10-1.30 (3H, m), 2.30-4.8 (17H, m),  
7.18-7.71 (13H, m)  
MASS (APCI): 511 (M+H)<sup>+</sup> (free)
- (9) (4R,8aS)-4-Benzhydryl-2-(2-ethoxy-4,6-dimethoxybenzyl)octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
10 NMR (DMSO-d<sub>6</sub>, δ): 1.10-1.30 (3H, m), 3.60 (3H, s), 3.79  
(3H, s), 2.30-4.8 (17H, m), 6.15-6.24 (2H, m),  
7.25-7.51 (10H, m)  
15 MASS (APCI): 487 (M+H)<sup>+</sup> (free)
- (10) (4R,8aS)-4-Benzhydryl-2-(2-isopropoxy-4,6-dimethoxybenzyl)octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
20 NMR (DMSO-d<sub>6</sub>, δ): 1.10-1.30 (6H, m), 3.55 (3H, s), 3.79  
(3H, s), 2.30-4.8 (16H, m), 6.18-6.20 (2H, m),  
7.25-7.51 (10H, m)  
MASS (APCI): 501 (M+H)<sup>+</sup> (free)
- (11) (4R,8aS)-4-Benzhydryl-2-[5-(1H-imidazol-1-yl)-2-methoxybenzyl]octahydropyrrolo[1,2-a]pyrazine trihydrochloride  
25 NMR (DMSO-d<sub>6</sub>, δ): 1.50-5.20 (18H, m), 7.10-8.00 (13H,  
m), 7.97 (1H, s), 8.24 (1H, s), 9.71 (1H, s)  
30 MASS (APCI): 479 (M+H)<sup>+</sup> (free)
- (12) (4R,8aS)-4-[Bis(4-fluorophenyl)methyl]-2-[2-methoxy-5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
35

IR (KBr, FT-IR): 1605, 1505, 1320, 1265, 1230  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 1.40-4.80 (15H, m), 3.80 (3H, s),  
7.06-7.95 (11H, m)

MASS (APCI): 585 ( $\text{M}+\text{H}$ )<sup>+</sup> (free)

5

(13) (1R or 1S, 4R, 8aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1-methyloctahydropyrrolo[1,2-a]pyrazine dihydrochloride

10 NMR (HCl free) ( $\text{CDCl}_3$ ,  $\delta$ ): 0.97-1.01 (3H, d,  $J=6.5\text{Hz}$ ),  
1.36-1.70 (7H, m), 2.12 (1H, dd,  $J=3.4, 12.0\text{Hz}$ ),  
2.31 (1H, dd,  $J=10.4, 12.0\text{Hz}$ ), 2.49 (1H, m), 2.73  
(1H, m), 2.93 (1H, ddd,  $J=3.1, 6.5\text{Hz}$ ), 3.12 (1H,  
ddd,  $J=3.4, 7.5, 10.3\text{Hz}$ ), 3.48 (1H, d,  $J=16.0\text{Hz}$ )  
MASS (APCI): 563 ( $\text{M}+\text{H}$ )<sup>+</sup> (free)

15

(14) (1S or 1R, 4R, 8aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1-methyloctahydropyrrolo[1,2-a]pyrazine dihydrochloride

20 NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 0.85-4.55 (22H, m), 7.08-7.63 (13H,  
m)

MASS (APCI): 563 ( $\text{M}+\text{H}$ )<sup>+</sup> (free)

(15) (4R, 7R, 8aS)-4-Benzhydryl-7-methoxy-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-

25 yl]benzyl]octahydropyrrolo[1,2-a]pyrazine  
dihydrochloride

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ): 1.90-5.00 (14H, m), 3.05 (3H, s),  
3.76 (3H, s), 6.90-7.80 (13H, m)

MASS (APCI): 579 ( $\text{M}+\text{H}$ )<sup>+</sup> (free)

30

(16) N-[(4R, 7S, 8aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazin-7-yl]-N,N-dimethylamine trihydrochloride

35 IR (KBr): 3400, 2900-2500, 1617, 1504, 1454  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.90-5.00 (20H, m), 3.80 (3H, s),  
7.19-7.37 (11H, m), 7.80-7.90 (2H, m), 10.00-  
11.80 (3H, m)

MASS (APCI): 592 (M+H)<sup>+</sup> (free)

5

(17) (4R, 7S, 8aS)-4-Bnzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-  
octahydropyrrolo[1,2-a]pyrazin-7-amine  
trihydrochloride

10 IR (KBr): 3400, 2900-2500, 1617, 1504, 1454 cm<sup>-1</sup>

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.00-4.50 (15H, m), 3.76 (3H, s),  
7.21-7.81 (13H, m), 8.16 (3H, br s)

MASS (APCI): 564 (M+H)<sup>+</sup> (free)

15 (18) (4R, 7S, 8aS)-4-Benzhydryl-7-fluoro-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.90-5.00 (14H, m), 3.82 (3H, s),  
6.90-7.80 (13H, m)

20 MASS (APCI): 567 (M+H)<sup>+</sup> (free)

(19) (4S, 7R, 8aS)-4-Benzhydryl-7-methoxy-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-  
octahydropyrrolo[1,2-a]pyrazine dihydrochloride

25 IR (KBr): 3400, 2900-2500, 1617, 1504, 1454 cm<sup>-1</sup>

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.90-5.00 (14H, m), 3.03 (3H, s),  
3.82 (3H, s), 6.90-7.80 (13H, m)

MASS (APCI): 579 (M+H)<sup>+</sup> (free)

30 (20) (4R, 8S, 8aR)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazin-8-ol  
dihydrochloride

35 NMR (DMSO- $d_6$ ,  $\delta$ ): 2.84-4.55 (20H, m), 7.22-7.68 (13H, m)



MASS (APCI) 565 (M+1) (free)

(21) (4R, 8S, 8aR)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-

5 yl]benzyl]octahydropyrrolo[1,2-a]pyrazin-8-ol

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.25-1.59 (2H, m), 1.84-2.17 (4H, m),  
2.38-2.67 (3H, m), 2.95-3.00 (1H, m), 3.42-3.63  
(3H, m), 3.80 (3H, s), 3.90-3.97 (2H, m), 6.90-  
7.45 (13H, m)

10 MASS (APCI): 565 (M+1)

#### Example 40

(4R, 7R, 8aS)-4-Benzhydryl-7-[(tert-butyldimethylsilyl)-  
oxy]-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-  
15 yl]benzyl]octahydropyrrolo[1,2-a]pyrazine (0.17 g) was  
dissolved in 1M tetrabutylammonium fluoride in  
tetrahydrofuran solution (1 ml) and the whole was stirred  
at room temperature for 4 hours. The mixture was poured  
into water and extracted with ethyl acetate. The extract  
20 was dried over magnesium sulfate and concentrated under  
reduced pressure. The syrup was purified by column  
chromatography on silica gel using a mixed solvent of  
dichloromethane and methanol (100:1). The fractions  
containing the objective compound were collected and  
25 treated with 4N hydrogen chloride in ethyl acetate to give  
the following compounds.

(1) (4R, 7R, 8aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-

30 octahydropyrrolo[1,2-a]pyrazine-7-ol dihydrochloride

IR (KBr): 3400, 2700-2500, 1508 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.00-5.00 (14H, m), 3.75 (3H, s),  
7.16-7.80 (13H, m)

MASS (APCI): 565 (M+H)<sup>+</sup> (free)

- (2) (4S, 7R, 8aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-octahydropyrrolo[1,2-a]pyrazin-7-ol dihydrochloride  
IR (KBr): 3400, 1504  $\text{cm}^{-1}$   
5 NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 1.95-2.00 (2H, m), 2.90-5.00 (12H, m),  
3.84 (3H, s), 7.00-8.00 (13H, m)  
MASS (APCI): 565 (M+H)<sup>+</sup> (free)

#### Example 41

- 10 The following compounds were obtained according to a similar manner to that of Example 22.

- (1) (4R, 7S, 8aS)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-octahydropyrrolo[1,2-a]pyrazin-7-ol dihydrochloride  
15 NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 1.37 (1H, m), 2.69-2.80 (2H, m),  
3.20-4.30 (17H, m), 7.16-7.72 (13H, m)  
MASS (APCI): 565 (M+H)<sup>+</sup> (free)
- 20 (2) (4R, 7S, 8aS)-4-Benzhydryl-7-methoxy-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 2.25-4.60 (22H, m), 7.17-7.77 (13H, m)  
25 MASS (APCI): 579 (M+H)<sup>+</sup> (free)
- (3) (4R, 7R, 8aS)-4-Benzhydryl-7-fluoro-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-octahydropyrrolo[1,2-a]pyrazine dihydrochloride  
30 NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 2.16-4.30 (19H, m), 7.20-8.04 (13H, m)  
MASS (APCI): 567 (M+H)<sup>+</sup> (free)

#### Example 42

- 35 To a solution of (2S)-2-[[N-(2-methoxybenzyl)-N-(2-

oxo-3,3-diphenylpropyl)amino]methyl]piperazine-1,4-dicarboxylic acid 4-N-benzyl ester 1-N-tert-butyl ester (3.15 g) in ethyl acetate (15 ml) was added a solution of 4N hydrogen chloride in ethyl acetate (29.6 ml) under ice-cooling. After stirring at the same temperature for 3 hours, the reaction mixture was evaporated under reduced pressure. To the solution of the residue in dichloromethane (30 ml) was added portionwise sodium triacetoxyborohydride (2.95 g) under ice-cooling, and then it was stirred at the same temperature for 20 hours. The mixture was poured into aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (5.2 g) using a mixed solvent of hexane and ethyl acetate (2:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (4S,9aS)-8-(benzyloxycarbonyl)-4-benzhydryl-2-(2-methoxybenzyl)octahydro-2H-pyrazino[1,2-a]pyrazine (2.0 g) as a syrup.

NMR (CDCl<sub>3</sub>, δ): 3.68 (3H, s), 1.75-4.25 (15H, m), 5.08 (2H, s), 6.70-6.90 (2H, m), 7.10-7.40 (17H, m)

MASS (APCI): 562 (M+H)<sup>+</sup>

25

#### Example 43

The following compound was obtained according to a similar manner for Example 42 from tert-butyl (2R,3S)-3-hydroxy-2-[[N-(2-methoxybenzyl)-N-(2-oxo-3,3-diphenylpropyl)amino]methyl]-1-pyrrolidinecarboxylate.

30

(4R,8S,8aR)-4-Benzhydryl-2-(2-methoxybenzyl)octahydropyrrolo[1,2-a]pyrazin-8-ol

NMR (DMSO-d<sub>6</sub>, δ): 1.91-4.29 (19H, m), 7.18-7.80 (13H, m)

35

MASS (APCI): 429 (M+1)

Example 44

The following compound was obtained according to a similar manner to that of Preparation 57 from (4R,8R,8aR)-8-azido-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazine.

(4R,8R,8aR)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazin-8-amine

NMR (CDCl<sub>3</sub>, δ): 1.22-2.21 (12H, m), 3.24-3.62 (4H, m), 3.81 (3H, s), 6.74-7.78 (13H, m)

MASS (APCI): 564 (M+1)

Example 45

The following compound was obtained according to a similar manner to that of Preparation 65 from (4R,8R,8aR)-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazin-8-yl acetate.

(4R,8R,8aR)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazin-8-ol

NMR (CDCl<sub>3</sub>, δ): 1.29-2.05 (6H, m), 2.18-2.23 (2H, m), 2.48-2.54 (1H, br), 2.74 (1H, m), 2.92 (1H, m), 3.26 (1H, m), 3.42-3.61 (2H, d x 2, J=15.2Hz), 3.81 (3H, s), 4.06-4.18 (1H, m), 6.91-7.48 (13H, m)

MASS (APCI): 565 (M+1)

Dihydrochloride of the above compound

NMR (DMSO-d<sub>6</sub>, δ): 1.23-4.30 (20H, m), 7.21-7.56 (13H, m)

MASS (APCI): 565 (M+1) (free)

Example 46

The following compound was obtained according to a similar manner to that of Preparation 57 from (4R,8S,8aR)-8-azido-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazine.

(4R,8S,8aR)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydropyrrolo[1,2-a]pyrazin-8-amine

NMR (CDCl<sub>3</sub>,  $\delta$ ): 1.50-3.04 (12H, m), 3.34-3.65 (3H, m), 3.79 (3H, s), 4.03 (1H, m), 6.74-7.45 (13H, m)

MASS (APCI): 564 (M+1)

Example 47

The following compounds were obtained according to a similar manner to that of Example 25.

(1) (4R,9aR)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-8-propionyloctahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride

mp: 171-175°C

[ $\alpha$ ]<sub>D</sub><sup>29.9</sup>: -40.38° (C=0.26, MeOH)

IR (KBr): 3435, 1649, 1504, 1458, 1433, 1267, 1201, 1163, 1032 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 0.95 (3H, t, J=7.5Hz), 2.10-4.50 (17H, m) 3.83 (3H, s), 7.10-7.50 (11H, m), 7.70-7.90 (2H, m)

MASS (API-ES): 620 (M+H)<sup>+</sup> (free)

(2) (4R,9aR)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-8-(2-methylpropionyl)octahydro-2H-pyrazino[1,2-a]pyrazine

dihydrochloride

mp: 172-175°C

$[\alpha]_D^{29.9}$ : -42.27° (C=0.33, MeOH)

IR (KBr): 3435, 1649, 1506, 1448, 1265, 1199, 1163 cm<sup>-1</sup>

5 NMR (DMSO-d<sub>6</sub>, δ): 0.93 (6H, d, J=6.6Hz), 2.10-4.50 (16H, m), 3.82 (3H, s), 7.10-7.50 (11H, m), 7.70-7.90 (2H, m)

MASS (APCI): 634 (M+H)<sup>+</sup> (free)

10 (3) (4R,9aR)-4-Benzhydryl-8-butyryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride

mp: 162-166°C

$[\alpha]_D^{30.0}$ : -40.14° (C=0.36, MeOH)

15 IR (KBr): 3435, 1649, 1504, 1458, 1267, 1201, 1163, 1028 cm<sup>-1</sup>

MASS (API-ES): 634 (M+H)<sup>+</sup> (free)

20 NMR (DMSO-d<sub>6</sub>, δ): 0.85 (3H, t, J=7.5Hz), 1.40-1.60 (2H, m), 2.10-4.50 (17H, m), 3.79 (3H, s), 7.10-7.50 (11H, m), 7.70-7.90 (2H, m)

(4) (4R,9aR)-4-Benzhydryl-8-ethoxycarbonyl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride

25 mp: 153-156°C

$[\alpha]_D^{29.9}$ : -43.09° (C=0.34, MeOH)

IR (KBr): 3444, 2983, 1701, 1504, 1442, 1267, 1199, 1163 cm<sup>-1</sup>

30 NMR (DMSO-d<sub>6</sub>, δ): 1.14 (3H, t, J=7.0Hz), 2.10-4.50 (15H, m), 3.82 (3H, s), 4.01 (2H, q, J=7.0Hz), 7.10-7.50 (11H, m), 7.70-7.90 (2H, m)

MASS (API-ES): 636 (M+H)<sup>+</sup> (free)

35 (5) (4R,9aR)-4-Benzhydryl-8-isopropoxycarbonyl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-

yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine  
dihydrochloride

mp: 147-150°C

$[\alpha]_D^{29.9}$ : -43.23° (C=0.325, MeOH)

5 IR (KBr): 3442, 2985, 1701, 1506, 1462, 1429, 1269,  
1199, 1161 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 1.16 (6H, d, J=6.8Hz), 2.20-4.80 (15H,  
m), 3.81 (3H, s), 4.73 (1H, m), 7.10-7.50 (11H,  
m), 7.70-7.90 (2H, m)

10 MASS (APCI): 650 (M+H)<sup>+</sup> (free)

#### Example 48

The following compound was obtained according to a  
similar manner to that of Preparation 94.

15

(4R, 9aR)-4-Benzhydryl-2-[2-methoxy-5-[5-  
(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-8-(3-  
methylbutyryl)octahydro-2H-pyrazino[1,2-a]pyrazine  
dihydrochloride

20 mp: 138-150°C, decomp.

$[\alpha]_D^{27}$ : -43.70 (C, 0.09, MeOH)

IR (KBr): 1649 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 0.66 (6H, d, J=1.7Hz), 1.71-4.30 (18H,  
m), 3.59 (3H, s), 7.07-7.58 (13H, m)

25 MASS (APCI+): 648.2 (MH<sup>+</sup>) (free)

#### Example 49

Formic acid (28 μl) was added to a mixture of  
(4R, 9aS)-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-  
30 1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-  
a]pyrazine trihydrochloride (100 mg), N,N-  
diisopropylethylamine (129 μl), 1-hydroxybenzotriazole  
(30.1 mg) and 1-[3-(dimethylamino)propyl]-3-  
ethylcarbodiimide hydrochloride (34.2 mg) in  
35 dichloromethane (2.0 ml). After being stirred for 18 hours

at room temperature, the resulting mixture was poured into water, and the whole was extracted with ethyl acetate, dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixed solvent of dichloromethane and methanol (20:1). The fractions containing the objective compound was collected and evaporated under reduced pressure and resulting residue was treated with 4N hydrogen chloride in ethyl acetate to give (6R,9aR)-6-benzhydryl-8-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbaldehyde dihydrochloride (100.1 mg) as colourless powder.

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.30-4.30 (21H, m), 7.18-8.00 (13H, m)

MASS (APCI): 592 (M+H)<sup>+</sup> (free)

#### Example 50

The following compound was obtained according to a similar manner to that of Example 4.

(4R,9aR)-4-Benzhydryl-8-isopropyl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine trihydrochloride

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.22-1.26 (6H, m), 2.20-4.56 (22H, m), 7.22-7.86 (13H, m)

MASS (APCI): 606 (M+H)<sup>+</sup> (free)

#### Example 51

Methanesulfonyl chloride (22.1 mg) was added to a mixture of (4R,9aS)-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine trihydrochloride (100 mg) and N,N-diisopropylethylamine (116  $\mu$ l) in dichloromethane under ice-cooling. After being stirred at the same temperature



for 2 hours the mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulphate, and evaporated under reduced pressure. The resulting oil was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol. The fractions containing the objective compound was collected and evaporated under reduced pressure and the resulting residue was treated with 4N hydrogen chloride in ethyl acetate to give (4R,9aR)-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride (52.8 mg) as colourless powder.

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 2.49-4.31 (23H, m), 7.17-7.80 (13H, m)

MASS: (APCI): 642 (M+H)<sup>+</sup> (free)

#### Example 52

The following compounds were obtained according to a similar manner to that of Example 51.

20

(1) (4R,9aR)-4-Benzhydryl-8-ethylsulfonyl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride

25

mp: 143-146°C

$[\alpha]_D^{30.0}$ : -43.33° (C=0.36, MeOH)

IR (KBr): 3435, 1506, 1458, 1329, 1267, 1199, 1159 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.15 (3H, t, J=7.3Hz), 2.20-4.50 (17H, m), 3.84 (3H, s), 7.10-7.50 (11H, m), 7.70-7.90

30

(2H, m)

MASS (API-ES): 656 (M+H)<sup>+</sup> (free)

35

(2) (4R,9aR)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-8-propylsulfonyloctahydro-2H-pyrazino[1,2-a]pyrazine

dihydrochloride

mp: 146-165°C

$[\alpha]_D^{28}$ : -40.40 (C=0.125, MeOH)

IR (KBr): 1508  $\text{cm}^{-1}$

5 NMR (DMSO- $d_6$ ,  $\delta$ ): 0.93 (3H, t,  $J=7.25\text{Hz}$ ), 1.50-1.75 (2H, m), 2.30-4.40 (17H, m), 3.83 (3H, s), 7.16-7.82 (13H, m)

MASS (APCI+): 670.0 (MH+) (free)

10 (3) (4R,9aR)-4-Benzhydryl-8-isopropylsulfonyl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride

mp: 150-155°C

15  $[\alpha]_D^{30.3}$ : -43.09° (C=0.55, MeOH)

IR (KBr): 3435, 1504, 1458, 1323, 1267, 1201, 1163  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.16 (6H, d,  $J=6.8\text{Hz}$ ), 2.20-4.50 (16H, m), 3.84 (3H, s), 7.10-7.50 (11H, m), 7.70-7.90 (2H, m)

20 MASS (APCI): 670 (M+H)<sup>+</sup> (free)

(4) (4R,9aR)-4-Benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-8-(2,2,2-trifluoroethylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride

25 IR (KBr): 1510  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 2.20-4.56 (17H, m), 3.84 (3H, s), 7.17-7.83 (13H, m)

MASS (APCI+): 710.1 (MH+) (free)

30

#### Example 53

The following compound was obtained according to a similar manner to that of Example 24.

35 (4R,9aS)-4-Benzhydryl-2-(2-methoxybenzyl)octahydro-2H-

pyrazino[1,2-a]pyrazine

NMR (CDCl<sub>3</sub>,  $\delta$ ): 3.67 (3H, s), 1.50-4.30 (16H, m), 6.70-6.90 (2H, m), 7.10-7.35 (12H, m)

MASS (APCI): 428 (M+H)<sup>+</sup>

5

#### Example 54

The following compound was obtained according to a similar manner to that of Example 25.

10 (4R,9aR)-8-Acetyl-4-benzhydryl-2-(2-methoxybenzyl)octahydro-2H-pyrazino[1,2-a]pyrazine

NMR (CDCl<sub>3</sub>,  $\delta$ ): 3.60-3.70 (3H, m), 1.70-4.00 (16H, m), 4.05-4.30 (2H, m), 6.70-6.95 (2H, m), 7.09-7.35 (12H, m)

15 MASS (APCI): 470 (M+H)<sup>+</sup>

#### Example 55

The following compounds were obtained according to a similar manner to that of Example 2.

20

(1) (4R,9aR)-8-Acetyl-4-benzhydryl-2-[2-methoxy-5-(trifluoromethyl)benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride

mp: 143-145°C

25  $[\alpha]_D^{30.0}$ : -54.35° (C=0.85, MeOH)

IR (KBr): 3435, 1647, 1502, 1431, 1255, 1159 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ): 1.98 (3H, m), 2.20-5.10 (18H, m), 7.00-7.60 (13H, m)

MASS (APCI): 554 (M+H)<sup>+</sup> (free)

30

(2) (4R,9aR)-8-Acetyl-4-benzhydryl-2-[2-methoxy-5-(4-pyridyl)benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine trihydrochloride

mp: 210-215°C

35  $[\alpha]_D^{30.1}$ : -47.25° (C=0.60, MeOH)

IR (KBr): 3435, 1639, 1606, 1495, 1448, 1277, 1147  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 1.99 (3H, s), 2.20-4.80 (18H, m),  
7.05-7.45 (11H, m), 8.13 (1H, d,  $J=8.9\text{Hz}$ ), 8.40-8.50  
(3H, m), 8.98 (2H, d,  $J=6.7\text{Hz}$ )

5 MASS (APCI): 547 (M+H)<sup>+</sup> (free)

(3) (4R,9aR)-8-Acetyl-4-benzhydryl-2-[2-ethoxy-5-[5-  
(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-  
2H-pyrazino[1,2-a]pyrazine dihydrochloride

10 mp: 162-165°C

$[\alpha]_D^{30.3}$ : -47.00° (C=0.80, MeOH)

IR (KBr): 3435, 1647, 1504, 1444, 1431, 1265, 1201,  
1163, 1036  $\text{cm}^{-1}$

15 NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 1.24-1.32 (3H, m), 1.94-1.99 (3H, m),  
2.20-4.60 (17H, m), 7.10-7.50 (11H, m), 7.70-7.90  
(2H, m)

MASS (API-ES): 620 (M+H)<sup>+</sup> (free)

20 (4) (4R,9aR)-8-Acetyl-4-benzhydryl-2-[2-methoxy-5-(1H-  
imidazol-1-yl)benzyl]octahydro-2H-pyrazino[1,2-  
a]pyrazine trihydrochloride

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 1.90-1.99 (3H, m), 2.20-4.60 (18H, m),  
7.10-7.50 (11H, m), 7.83 (1H, d,  $J=8.9\text{Hz}$ ), 7.97  
(1H, s), 8.13 (1H, s), 8.29 (1H, s), 9.71 (1H, s)

25 MASS (APCI): 536 (M+H)<sup>+</sup> (free)

(5) (4R,9aR)-8-Acetyl-4-benzhydryl-2-[2-methoxy-5-  
(trifluoromethyl)benzyl]octahydro-2H-pyrazino[1,2-  
a]pyrazine dihydrochloride

30 mp: 147-150°C

$[\alpha]_D^{30.3}$ : -53.46° (C=0.26, MeOH)

IR (KBr): 3435, 1626, 1448, 1333, 1269, 1165, 1122  $\text{cm}^{-1}$

35 NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 1.91-1.99 (3H, m), 2.20-4.40 (18H, m),  
7.10-7.50 (11H, m), 7.75 (1H, d,  $J=8.8\text{Hz}$ ), 7.87  
(1H, s)

MASS (APCI): 538 (M+H)<sup>+</sup> (free)

(6) (4R,9aR)-8-Acetyl-4-benzhydryl-2-[2-methoxy-5-(furan-3-yl)benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride

mp: 173-177°C

[α]<sub>D</sub><sup>30.3</sup>: -57.27° (C=0.75, MeOH)

IR (KBr): 3435, 1645, 1512, 1448, 1431, 1259, 1151, 1022 cm<sup>-1</sup>

MASS (APCI): 536 (M+H)<sup>+</sup> (free)

NMR (DMSO-d<sub>6</sub>, δ): 1.91-1.99 (3H, m), 2.20-4.50 (18H, m), 6.92 (1H, s), 6.98-7.45 (11H, m), 7.61 (1H, d, J=8.9Hz), 7.75 (1H, s), 7.84 (1H, d, J=5.5Hz), 8.06 (1H, s)

(7) (4R,9aR)-8-Acetyl-4-benzhydryl-2-[(4-methoxypyridin-3-yl)methyl]octahydro-2H-pyrazino[1,2-a]pyrazine trihydrochloride

mp: 205-210°C

[α]<sub>D</sub><sup>30.2</sup>: -62.83° (C=0.60, MeOH)

IR (KBr): 3435, 1641, 1502, 1448, 1431, 1267, 1238 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 1.91-1.99 (3H, m), 2.20-4.60 (18H, m), 7.10-7.70 (11H, m), 8.84 (2H, m)

MASS (APCI): 471 (M+H)<sup>+</sup> (free)

(8) (4R,9aR)-8-Acetyl-4-benzhydryl-2-[2-isopropoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride

mp: 167-171°C

[α]<sub>D</sub><sup>30.2</sup>: -37.44° (C=0.45, MeOH)

IR (KBr): 3435, 2981, 1649, 1502, 1431, 1265, 1201, 1165 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 1.17-1.30 (6H, m), 1.90-1.99 (3H, m), 2.20-4.90 (16H, m), 7.10-7.50 (11H, m), 7.70-7.90 (2H, m)

MASS (API-ES): 634 (M+H)<sup>+</sup> (free)

- (9) (4R,9aR)-8-Acetyl-4-benzhydryl-2-(2,4,6-trimethoxybenzyl)octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride  
5 mp: 170-173°C  
[α]<sub>D</sub><sup>30.0</sup>: -67.35° (C=0.66, MeOH)  
IR (KBr): 3435, 1647, 1610, 1462, 1427, 1234, 1147, 1041 cm<sup>-1</sup>  
10 NMR (DMSO-d<sub>6</sub>, δ): 1.96 (3H, s), 2.10-4.50 (15H, m), 3.66 (3H, s), 3.68 (3H, s), 3.80 (3H, s), 6.21 (1H, s), 6.23 (1H, s), 7.10-7.50 (10H, m)  
MASS (API-ES): 530 (M+H)<sup>+</sup> (free)
- (10) (4R,9aR)-8-Acetyl-4-benzhydryl-2-(2-ethoxy-6-methoxybenzyl)octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride  
15 IR (KBr): 3435, 1647, 1599, 1468, 1255, 1122 cm<sup>-1</sup>  
NMR (DMSO-d<sub>6</sub>, δ): 1.15-1.30 (3H, m), 1.90-2.00 (3H, m),  
20 2.20-4.50 (20H, m), 6.60-6.70 (2H, m), 7.10-7.50 (11H, m)  
MASS (APCI): 514 (M+H)<sup>+</sup> (free)
- (11) (4R,9aR)-8-Acetyl-4-benzhydryl-2-(2-isopropoxy-6-methoxybenzyl)octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride  
25 IR (KBr): 3435, 2976, 1651, 1595, 1469, 1431, 1255, 1117 cm<sup>-1</sup>  
NMR (DMSO-d<sub>6</sub>, δ): 1.10-1.25 (6H, m), 1.95-2.00 (3H, m),  
30 2.20-4.65 (19H, m), 6.59-6.70 (2H, m), 7.10-7.50 (11H, m)  
MASS (APCI): 528 (M+H)<sup>+</sup> (free)
- (12) (4R,9aR)-8-Acetyl-4-benzhydryl-2-(2-ethoxy-4,6-dimethoxybenzyl)octahydro-2H-pyrazino[1,2-a]pyrazine  
35

dihydrochloride

IR (KBr): 3435, 2975, 1647, 1606, 1460, 1429, 1232,  
1146  $\text{cm}^{-1}$

5 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.05-1.25 (3H, m), 1.96-2.00 (3H, m),  
3.79 (3H, s), 2.20-4.70 (20H, m), 6.18-6.22 (2H,  
m), 7.10-7.50 (10H, m)

MASS (APCI): 543 (M)<sup>+</sup> (free)

10 (13) (4R,9aR)-8-Acetyl-4-benzhydryl-2-[2-methoxy-5-(3-  
thienyl)benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine  
dihydrochloride

mp: 177-181°C

$[\alpha]_D^{29.9}$ : -55.69° (C=0.29, MeOH)

15 IR (KBr): 3425, 1647, 1498, 1444, 1429, 1259, 1142,  
1022  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ): 1.99 (3H, s), 2.10-5.30 (18H, m),  
7.00-8.05 (16H, m)

MASS (APCI): 552 (M+H)<sup>+</sup> (free)

20 (14) (4R,9aR)-8-Acetyl-4-benzhydryl-2-(2-isopropoxy-4,6-  
dimethoxybenzyl)octahydro-2H-pyrazino[1,2-a]pyrazine  
dihydrochloride

IR (KBr): 3400, 1645, 1610, 1454, 1427, 1203, 1151,  
1132  $\text{cm}^{-1}$

25 NMR (DMSO- $d_6$ ,  $\delta$ ): 1.10-1.24 (6H, m), 1.91-2.00 (3H, m),  
3.79 (3H, s), 2.20-4.80 (19H, m), 6.19-6.22 (2H,  
s), 7.10-7.45 (10H, m)

MASS (API-ES): 558 (M+H)<sup>+</sup> (free)

30 Example 56

Diisopropylethylamine (0.236 ml) was added to an ice-  
cooled solution of 1-[3-(bromomethyl)-4-fluorophenyl]-5-  
(trifluoromethyl)-1H-tetrazole and in N,N-dimethylformamide  
(2 ml) and the mixture was stirred for 3 hours at room  
35 temperature. The mixture was washed with aqueous sodium

hydrogen carbonate. The organic layer was separated, dried over magnesium sulfate, and evaporated under reduced pressure. The syrup was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (100:1 - 40:1). The fractions containing the objective compound were collected to give a syrup. The syrup was treated with 4N hydrogen chloride in ethyl acetate solution to give (4R,8aS)-4-benzhydryl-2-[2-fluoro-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-octahydropyrrolo[1,2-a]pyrazine dihydrochloride (0.22 g).

IR (KBr): 3400, 2800-2500, 1533  $\text{cm}^{-1}$   
NMR (DMSO- $d_6$ ,  $\delta$ ): 1.50-5.00 (13H, m), 7.15-8.00 (13H, m), 11.50-12.00 (2H, m)  
MASS (APCI): 537 (M+H)<sup>+</sup> (free)

15

Example 57

The following compound was obtained according to a similar manner to that of Example 56.

(4R,9aR)-8-Acetyl-4-benzhydryl-2-[2-fluoro-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride

IR (KBr): 3400, 2800-2500, 1533  $\text{cm}^{-1}$   
NMR (DMSO- $d_6$ ,  $\delta$ ): 1.95-2.00 (3H, m), 2.20-5.20 (15H, m), 7.13-8.00 (13H, m)  
MASS (APCI): 594 (M+H)<sup>+</sup> (free)

25

Example 58

To a solution of 2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzaldehyde (582 mg) and (4S,9aS)-4-benzhydryl-8-(benzyloxycarbonyl)octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride (1.0 g) in dichloromethane (10 ml) was added portionwise sodium tritacetoxyborohydride (824 mg) under ice-cooling, and then it was stirred at room temperature for 90 minutes. The mixture was poured into

35



aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (23 g) using a mixed solvent of hexane and ethyl acetate (2:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (4S,9aS)-4-benzhydryl-8-benzyloxycarbonyl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine (0.98 g) as a colorless foam.

NMR (CDCl<sub>3</sub>, δ): 3.81 (3H, s), 1.80-4.25 (15H, m), 5.08 (2H, s), 6.92 (1H, d, J=8.7Hz), 7.05-7.40 (17H, m)

MASS (APCI): 698 (M+H)<sup>+</sup>

#### Example 59

(4S,9aS)-4-Benzhydryl-8-benzyloxycarbonyl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine (187 mg) was dissolved in tetrahydrofuran (2 ml), and triethylamine (0.0747 ml) was added to it at room temperature. The solution was hydrogenated over 10% palladium-charcoal (50% wet, 40 mg) at room temperature under atmospheric pressure for 2 hours. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure to give colorless syrup. The resulting residue was purified by column chromatography on silica gel (7 g) using a mixed solvent of dichloromethane and methanol (10:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give a syrup. To a solution of the syrup in dichloromethane (2 ml) was added a solution of 4N hydrogen chloride in ethyl acetate (0.050 ml), and triturated with diisopropyl ether. The precipitate was collected by filtration and dried under

reduced pressure for 5 hours at 40°C to give (4S,9aR)-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine trihydrochloride (154 mg) as a colorless powder.

5       NMR (DMSO-d<sub>6</sub>, δ): 3.82 (3H, s), 2.15-4.70 (15H, m),  
7.15-7.40 (11H, m), 7.75-7.90 (2H, m), 9.43 (2H, br)

MASS (APCI): 564 (M+H)<sup>+</sup> (free)

10   Example 60

(4S,9aS)-4-Benzhydryl-8-benzyloxycarbonyl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine (740 mg) was dissolved in tetrahydrofuran (8 ml), and triethylamine  
15 (0.296 ml) was added to it at room temperature. The solution was hydrogenated over 10% palladium-charcoal (50% wet, 150 mg) at room temperature under atmospheric pressure for 2 hours. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure to give  
20 a colorless syrup. To a solution of the syrup in dichloromethane (10 ml) was added N,N-diisopropylethylamine (0.374 ml) and acetyl chloride (0.114 ml) under ice-cooling. After stirred at the same temperature for 2 hours, the mixture was poured into aqueous sodium hydrogen carbonate  
25 and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (10 g) using a mixed solvent of dichloromethane and methanol  
30 (20:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give a syrup. To a solution of the syrup in ethyl acetate (3 ml) was added a solution of 4N hydrogen chloride in ethyl acetate (0.70 ml), and triturated with diisopropyl  
35 ether. The precipitate was collected by filtration and

dried under reduced pressure for 5 hours at 40°C to give  
(4S,9aS)-8-acetyl-4-benzhydryl-2-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]octahydro-2H-pyrazino[1,2-a]pyrazine dihydrochloride (580 mg) as a  
5 colorless powder.

NMR (DMSO-d<sub>6</sub>, δ): 1.90-2.00 (3H, m), 2.15-4.70 (18H, m),  
7.10-7.45 (11H, m), 7.70-7.90 (2H, m)

MASS (API-ES): 606 (M+H)<sup>+</sup> (free)

10 Example 61

The following compounds were obtained according to a similar manner to that of Example 2.

(1) 7-Benzhydryl-9-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-6,9-diazaspiro[4.5]decane  
15 dihydrochloride

IR (KBr): 3400-3200, 2900-2500, 1504 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 1.50-4.9 (19H, m), 7.09-8.20 (13H, m),  
8.90-9.10 (1H, m), 9.70-10.00 (2H, m)

20 MASS (APCI): 563 (M+H)<sup>+</sup> (free)

(2) 6-Benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-2,2-dimethylpiperazine  
25 dihydrochloride

IR (KBr): 3400-3100, 2900-2500, 1504, 1454 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ): 1.35 (3H, s), 1.50 (3H, s), 2.20-5.00  
(11H, m), 7.14-7.71 (14H, m), 9.80-10.20 (3H, m)

MASS (APCI): 537 (M+H)<sup>+</sup> (free)

30 Example 62

The following compounds were obtained according to a similar manner to that of Example 4.

(1) 7-Benzhydryl-9-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-6-methyl-6,9-  
35

diazaspiro[4.5]decane dihydrochloride

IR (KBr): 3400-3200, 2900-2500, 1504  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 1.50-4.9 (19H, m), 3.80 (3H, s),  
7.09-8.20 (13H, m), 8.50-8.60 (2H, m)

5 MASS (APCI): 577 (M+H)<sup>+</sup> (free)

(2) 6-Benzhydryl-4-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-1,2,2-trimethylpiperzine  
dihydrochloride

10 IR (KBr): 3400-3100, 2900-2500, 1504, 1454  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ): 1.35-1.50 (6H, m), 2.20-5.00 (14H, m),  
7.14-7.71 (13H, m)

MASS (APCI): 551 (M+H)<sup>+</sup> (free)

15

20

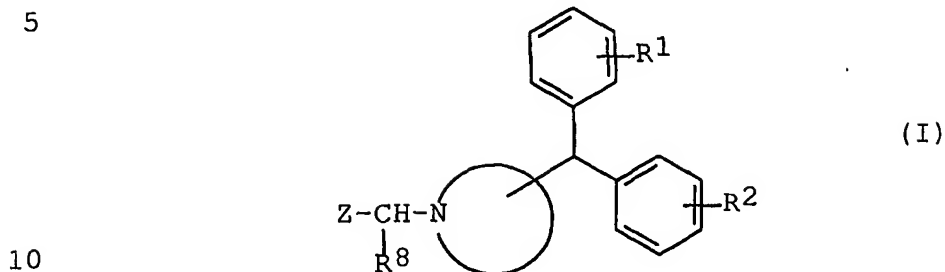
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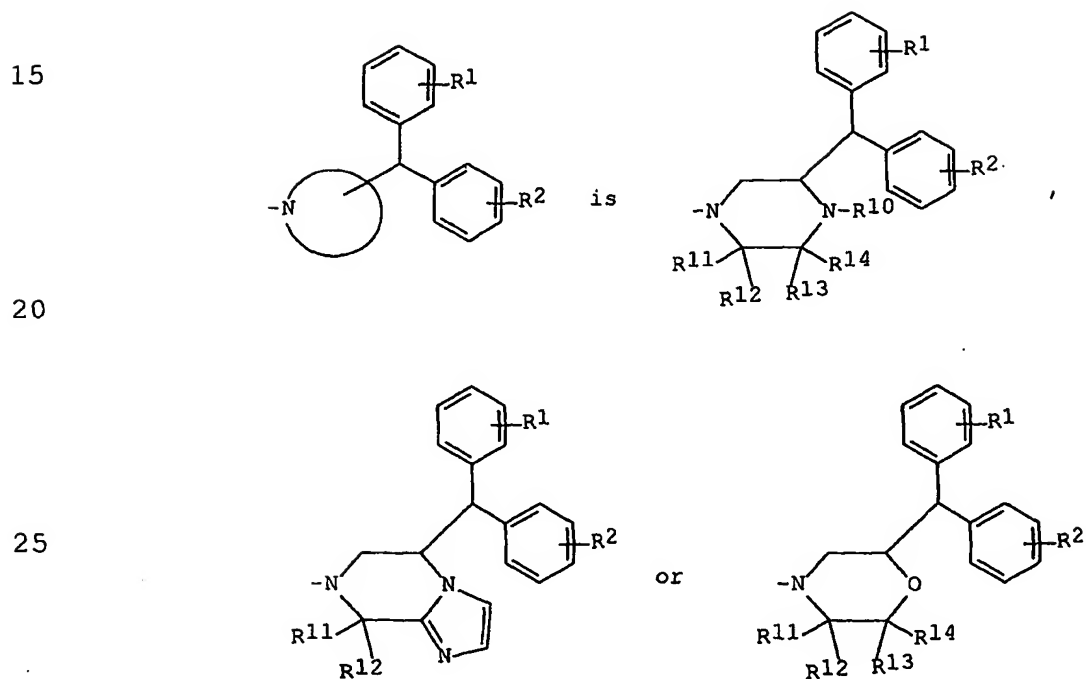
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## C L A I M S

1. A compound of the formula (I):

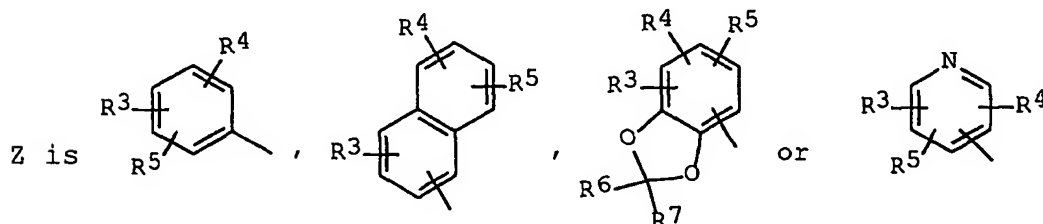


wherein



30 in which  $R^1$  and  $R^2$  are independently hydrogen, halogen, lower alkoxy, lower alkyl or mono(or di or tri)halo(lower)alkyl,  
 $R^{10}$  is hydrogen or lower alkyl optionally substituted with lower alkoxy, carbamoyl or phenyl,  
 35  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  are independently hydrogen,

lower alkoxycarbonyl or lower alkyl optionally substituted with hydroxy or lower alkoxy, and  $R^{10}$  and  $R^{14}$  optionally forming  $-(CH_2)_i-CHR^{15}-(CH_2)_j-$ ,  $-(CH_2)_i-NR^{16}-(CH_2)_j-$ ,  $-(CH_2)_i-O-CH_2-CO-$  or  $-(CH_2)_i-O-(CH_2)_j-$ , wherein  $i$  and  $j$  are independently 1 or 2,  $R^{15}$  is hydrogen, halogen, lower alkyl, hydroxy, lower alkoxy, amino, lower alkylamino or di(lower)alkylamino and  $R^{16}$  is hydrogen, lower alkyl, lower alkanoyl, lower alkoxycarbonyl, benzyloxycarbonyl, lower alkylsulfonyl or mono(or di or tri)halo(lower)alkylsulfonyl, or  $R^{12}$  and  $R^{13}$  optionally forming  $-(CH_2)_i-CHR^{15}-(CH_2)_j-$ , wherein  $i$ ,  $j$  and  $R^{15}$  are defined as above, or  $R^{13}$  and  $R^{14}$  optionally forming oxo or two to five methylenes,



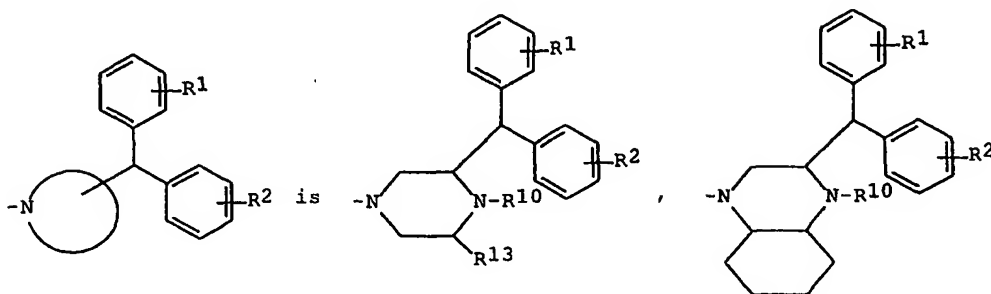
in which  $R^3$ ,  $R^4$  and  $R^5$  are independently hydrogen; halogen; lower alkyl, mono(or di or tri)halo(lower)alkyl; cyano; lower alkoxycarbonyl; lower alkylthio; lower alkylsulfonyl; hydroxy; lower alkoxy optionally substituted with lower alkoxy, lower alkoxycarbonyl, carbamoyl, cyano, phenyl or one, two or three halogen(s); lower alkenyloxy; cyclo(lower)alkyloxy; nitro; lower alkylamino; di(lower)alkylamino; or imidazolyl, pyrazolyl, thienyl, thiazolyl, furyl, tetrazolyl, pyridyl or phenyl, each of which may have a substituent selected from a group which consists of lower alkyl, mono(or di or tri)halo(lower)alkyl, lower alkylsulfonyl, lower alkylsulfinyl, lower alkylthio, lower alkylamino and

di(lower)alkylamino, and  
 $R^6$  and  $R^7$  are independently hydrogen or halogen, and  
 $R^8$  is hydrogen or lower alkyl,  
 and a salt thereof.

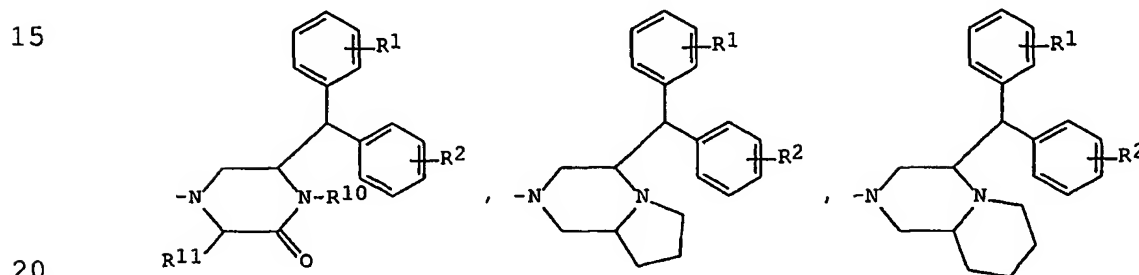
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2. The compound of claim 1, in which

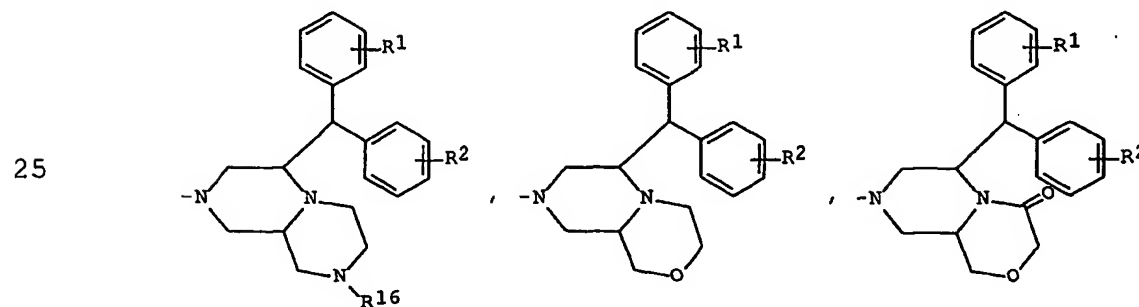
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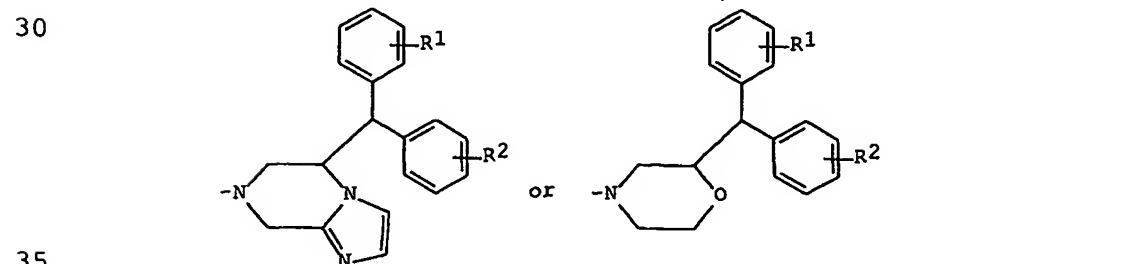
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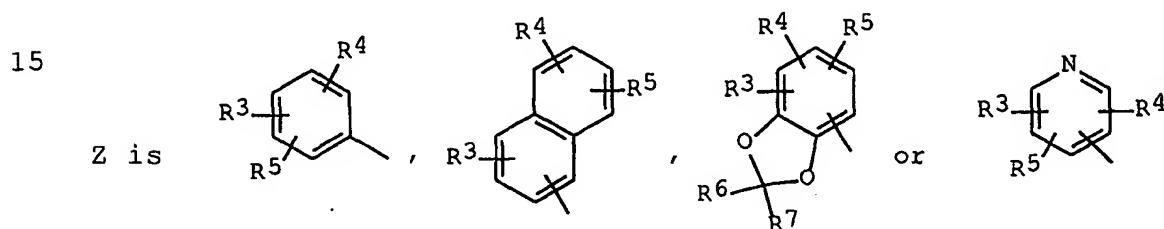
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in which  $R^1$  and  $R^2$  are independently hydrogen,  
 $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkyl or  
 mono(or di or tri)halo( $C_1$ - $C_4$ )alkyl,  
 5  $R^{10}$  is hydrogen or  $C_1$ - $C_4$  alkyl optionally substituted  
 with  $C_1$ - $C_4$  alkoxy, carbamoyl or phenyl,  
 $R^{11}$  and  $R^{13}$  are independently hydrogen,  $C_1$ - $C_4$   
 alkoxycarbonyl or  $C_1$ - $C_4$  alkyl optionally substituted  
 with hydroxy or  $C_1$ - $C_4$  alkoxy,  
 10  $R^{16}$  is hydrogen,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkanoyl,  $C_1$ - $C_4$   
 alkoxycarbonyl, benzyloxycarbonyl,  $C_1$ - $C_4$  alkylsulfonyl  
 or mono(or di or tri)halo( $C_1$ - $C_4$ )alkylsulfonyl,

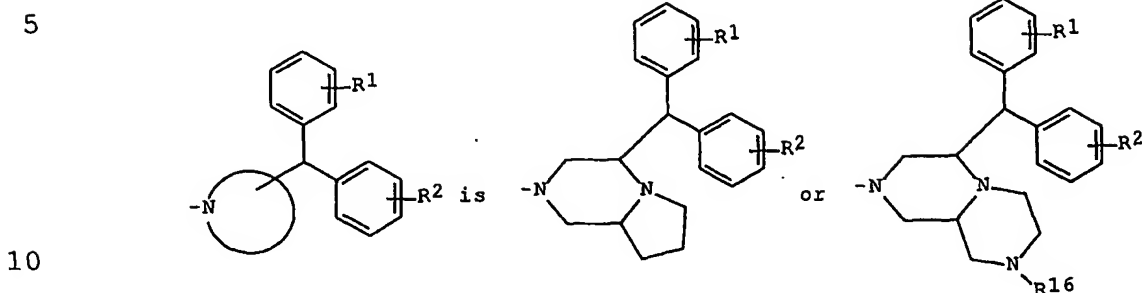


20 in which  $R^3$ ,  $R^4$  and  $R^5$  are independently hydrogen;  
 halogen;  $C_1$ - $C_4$  alkyl; mono(or di or tri)halo( $C_1$ - $C_4$ )-  
 alkyl; cyano;  $C_1$ - $C_4$  alkoxycarbonyl;  $C_1$ - $C_4$  alkylthio;  
 $C_1$ - $C_4$  alkylsulfonyl; hydroxy;  $C_1$ - $C_4$  alkoxy optionally  
 substituted with  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkoxycarbonyl,  
 25 carbamoyl, cyano, phenyl or one, two or three  
 halogen(s);  $C_2$ - $C_4$  alkenyloxy; cyclo( $C_3$ - $C_6$ )-  
 alkyloxy; nitro;  $C_1$ - $C_4$  alkylamino; di( $C_1$ -  
 $C_4$ )alkylamino; or imidazolyl, pyrazolyl, thienyl,  
 thiazolyl, furyl, tetrazolyl, pyridyl or phenyl, each  
 30 of which may have a substituent selected from a group  
 which consists of  
 $C_1$ - $C_4$  alkyl, mono(or di or tri)halo( $C_1$ - $C_4$ )alkyl,  $C_1$ - $C_4$   
 alkylsulfonyl,  $C_1$ - $C_4$  alkylsulfinyl,  $C_1$ - $C_4$  alkylthio,  
 $C_1$ - $C_4$  alkylamino and di( $C_1$ - $C_4$ )alkylamino, and  
 35  $R^6$  and  $R^7$  are independently hydrogen or halogen, and



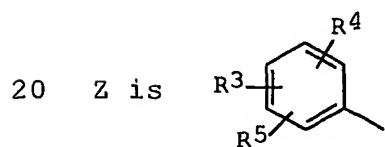
$R^8$  is hydrogen or  $C_1$ - $C_4$  alkyl.

3. The compound of claim 2, in which



in which  $R^1$  and  $R^2$  are independently hydrogen,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkyl or mono(or di or tri)halo( $C_1$ - $C_4$ )-alkyl, and

15  $R^{16}$  is hydrogen,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkanoyl,  $C_1$ - $C_4$  alkoxy carbonyl, benzyloxy carbonyl,  $C_1$ - $C_4$  alkylsulfonyl or mono(or di or tri)halo( $C_1$ - $C_4$ )alkylsulfonyl,



in which  $R^3$  is hydrogen,

$R^4$  is  $C_1$ - $C_4$  alkoxy, and

25  $R^5$  is imidazolyl, pyrazolyl, thienyl, thiazolyl, furyl, tetrazolyl, pyridyl or phenyl, each of which may have a substituent selected from a group which consists of  $C_1$ - $C_4$  alkyl, mono(or di or tri)halo( $C_1$ - $C_4$ )alkyl,  $C_1$ - $C_4$  alkylsulfonyl,  $C_1$ - $C_4$  alkylsulfinyl,  $C_1$ - $C_4$  alkylthio,

30  $C_1$ - $C_4$  alkylamino and di( $C_1$ - $C_4$ )alkylamino, and

$R^8$  is hydrogen or  $C_1$ - $C_4$  alkyl.

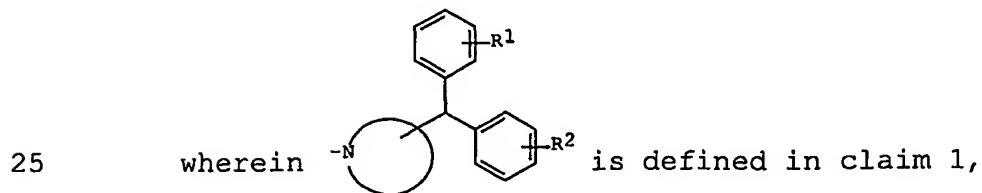
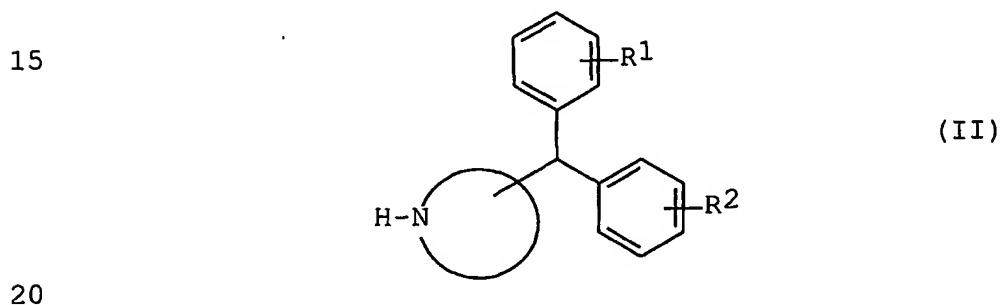
4. A compound of claim 3, which is selected from a group which consists of

35 (1) (4R,8aS)-4-Benzhydryl-2-[2-methoxy-5-[5-

(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]-  
 octahydropyrrolo[1,2-a]pyrazine, and  
 (2) 1-[(6R,9aR)-6-Benzhydryl-8-[2-methoxy-5-[5-  
 (trifluoromethyl)-1H-tetrazol-1-  
 yl]benzyl]octahydropyrazino[1,2-a]pyrazin-2-  
 yl]ethanone,  
 or a pharmaceutically acceptable salt thereof.

5. A process for the preparation of the compound of claim  
 1 or a salt thereof, which comprises,

(1) reacting a compound of the formula (II):



or its reactive derivative at the imino group  
 or a salt thereof, with a compound of the formula  
 (III):



wherein Z and  $\text{R}^8$  are each as defined in claim 1, or a  
 salt thereof to give a compound of the formula (I):

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